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Female Pelvic Floor Disorders – Clinical Aspects on Surgical Treatments

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“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”

– Marie Curie

To my mother,
for your enduring patience

ABSTRACT

Background and aims

The life-time risk for a woman to undergo pelvic floor reconstructive surgery due to prolapse or incontinence is 20% and the high risk for recurrence after prolapse surgery is a major challenge. Surgical reconstruction of the perineal body is commonly performed, although studies assessing results of this procedure are scarce. Mid-urethral sling surgery has a cure rate of 80%, but whether the sling endures a subsequent delivery is largely unknown. In this thesis we aimed to investigate whether the choice of suture material has an impact on vaginal wall prolapse repair; whether cervical amputation results in similar cure rates in comparison to vaginal hysterectomy in women with uterine prolapse; if a subsequent delivery jeopardizes results from incontinence surgery; if physiotherapy and surgical treatment is equally effective in women with symptoms related to a poorly healed second-degree perineal tear.

Methods and main results

Study I and II are both register-based cohort studies based on data from the Swedish National Quality Register for Gynecological Surgery (GynOp). In **Study I**, 731 women who underwent primary anterior colporrhaphy and 384 women who underwent primary posterior colporrhaphy were included. We found a significantly lower rate of women reporting vaginal bulging symptoms one year after anterior colporrhaphy if a slowly absorbable monofilament suture was used compared to a more rapidly absorbable multifilament suture, 22% vs 30% (aOR 1.6, 95% CI 1.1-2.3). There was no difference between the suture groups in the posterior colporrhaphy cohort. In **Study II,** women with uterine prolapse who had undergone either cervical amputation (n=1979) or vaginal hysterectomy (n=1195) were analyzed. There were no differences between the two groups regarding neither symptom relief nor patient satisfaction at one year after surgery. Vaginal hysterectomy was associated with a higher rate of severe complications compared to cervical amputation, 1.9 % vs 0.2 % ($p < 0.001$).

Study III is a cross-sectional, survey-based study. National registers were used to identify women with a delivery subsequent to a mid-urethral sling procedure (n=207) and a matched control-group including women without childbirth after a mid-urethral sling procedure (n=521). Validated questionnaires investigating urinary symptoms were mailed to the study participants. Patient reported stress urinary incontinence was present in 22% of the women with a delivery after a mid-urethral sling procedure and in 17% of the women in the control group (aOR 1.2, 95% CI 0.7-2.0). Vaginal childbirth after mid-urethral sling surgery did not increase the risk of stress urinary incontinence compared to cesarean delivery.

Study IV is a randomized controlled trial where 70 women with a poorly healed second degree perineal tear, minimum six months post-partum, were randomized to either surgery or tutored pelvic floor muscle therapy. In an intention-to-treat analysis with worst case outcome imputation, treatment success at 6 months follow-up was significantly more frequent in the surgery group, 71% vs 11%, $p<0.001$.

Conclusions

In conclusion, the use of slowly absorbable monofilament sutures in anterior colporrhaphy was associated with a lower risk of symptomatic prolapse at one year postoperatively, compared to more rapidly absorbable multifilament sutures. In women with uterine prolapse, cervical amputation seems to result in similar patient reported outcomes as compared to vaginal hysterectomy, but comes with a lower risk of severe complications. Childbirth after a mid-urethral sling procedure does not increase the risk for recurrent stress urinary incontinence and the mode of a subsequent delivery does not seem to impact continence status. Finally, surgical treatment was superior to pelvic floor muscle therapy in providing symptom relief in women with poorly healed second-degree perineal tears.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals. Papers protected by copyrights were reproduced with permission from the copyright holders.

I. Bergman I, Westergren Söderberg M, Kjaeldgaard A, Ek M

Does the choice of suture material matter in anterior and posterior colporrhaphy?

International Urogynecology Journal, 2016 Sep;27(9):1357-65

II. Bergman I, Westergren Söderberg M, Kjaeldgaard A, Ek M

Cervical amputation versus vaginal hysterectomy; a population-based register study

International Urogynecology Journal, 2017 Feb;28(2):257-266

III. Bergman I, Westergren Söderberg M, Lundqvist A, Ek M

Associasions between childbirth and urinary incontinence after mid-urethral sling surgery

Obstetrics and Gynecology. 2018 Feb;131(2):297-303

IV. Bergman I, Westergren Söderberg M, Ek M

Perineorrhaphy compared with pelvic floor muscle therapy in women with late consequences of a poorly healed second-degree perineal tear: a randomized controlled trial

Obstetrics and Gynecology, 2020 Feb 9. Epub ahead of print.

CONTENTS

LIST OF ABBREVIATIONS

AI	Anal incontinence
ATFP	Arcus tendinous fascia pelvis
BMI	Body mass index
CI	Confidence interval
ICS	International Continence Society
ISD	Intrinsic sphincter deficiency
IUGA	International Urogynecological Association
LUTS	Lower urinary tract symptoms
MBR	Medical Birth Register
MP	Manchester procedure
MRI	Magnetic resonance imaging
MUS	Mid-urethral sling
NPR	National Patient Register
OAB	Overactive bladder syndrome
OR	Odds ratio
PFMT	Pelvic floor muscle training
POP	Pelvic organ prolapse
POP-Q	Pelvic organ prolapse quantification system
SSLF	Sacrospinosus ligament fixation
SUI	Stress urinary incontinence
TVT	Transvaginal tape
TVT-O	Transvaginal tape, obturator approach
TVT-R	Transvaginal tape, retropubic approach
UI	Urinary incontinence
UUI	Urgency urinary incontinence
VH	Vaginal hysterectomy

1 INTRODUCTION

Urogynecology is a cross-disciplinary medical field dedicated to the care and management of functional pelvic floor disorders. The umbrella term *pelvic floor disorders* (used in the present thesis) is often used to describe conditions such as pelvic organ prolapse (POP), urinary incontinence (UI), anal incontinence (AI), pelvic floor muscle dysfunction, and various structural sequalae to the pelvic floor anatomy after childbirth.

Pelvic floor disorders share etiological and pathophysiological pathways and often co-exist or present with overlapping symptoms. Further, surgical treatment of one condition may affect symptoms of another condition, for example may POP surgery unmask occult stress urinary incontinence (SUI). The multifactorial origins of pelvic floor disorders is complex and involves an interaction between hereditary and environmental risk factors, as well as, a delay of symptom onset. Known risk factors that may be shared between different conditions such as POP, UI and AI include trauma at childbirth, menopause, aging, obesity and pelvic surgery.[1] Other risk factors that may influence the occurrence of pelvic floor disorders are for example smoking, physical labor, connective tissue disorders and chronic constipation or cough,[1] whereas genetic factors seems to have a considerable impact on both POP and SUI.[2,3]

Pelvic floor disorders also share common consequences and burden patients with often severe implications for daily function, social interactions, personal hygiene, sexuality, and mental wellbeing.[4] Thus, the consequences of pelvic floor dysfunction may impact and interfere with a wide range of aspects of women's individual quality of life.

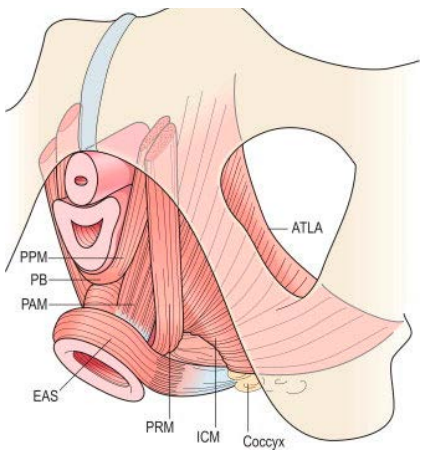
The estimated risk for a woman to undergo at least one reconstructive pelvic floor procedure during her lifetime is around 20%.[5,6] Unfortunately, recurrence of bothersome symptoms after surgery is common, and re-operation rates are as high as 27-30%.[7,8] In Sweden, 8,500 POP operations, 4,500 mid-urethral sling (MUS) procedures and 2,100 perineal reconstructions were performed in 2018.[9] Female pelvic floor dysfunction may thus be considered a public health problem and the already significant annual costs for pelvic reconstructive surgery will most likely double during the next decades because of an aging population.[10,11] The overarching aim of this thesis has been to identify variables that could optimize outcomes in women who undergo surgical treatment for symptoms related to pelvic floor dysfunction.

2 BACKGROUND

2.1 FUNCTIONAL PELVIC FLOOR ANATOMY

2.1.1 Levator ani and the endopelvic fascia

A band of connective tissue extends from the pubic bone to the ischial spines and forms the arcus tendineus fascia pelvis (ATFP), also known as the tendinous arch. The tendinous arch acts like a cable of a suspension bridge and provides attachment points for the supporting tissues of the pelvic floor. The levator ani muscle, which forms the muscular floor of the pelvis and plays a crucial role in supporting the female pelvic organs, consists of the iliococcygeus and the pubococcygeus muscle. The pubococcygeus muscle runs from the sacrum to the pubis and the anterior portion of the tendinous arch. The puborectalis forms a sling behind the anorectum and is an important structure in maintaining anal continence. By contracting, it pulls and sharply angulates the rectum, and when relaxing, the angle of fecal flow is straighter allowing evacuation. Various muscle subdivisions reflect the attachments of the muscle to the urethra, vagina, perineum, anus and rectum (pubourethralis, pubovaginalis, puboperinealis, puboanalis and puborectalis). The opening within the levator ani, through which the urethra and vagina pass, is called the urogenital hiatus. The muscles are contracted at rest and close the urogenital hiatus. The iliococcygeus muscles arise from the tendinous arch and attach to the coccyx. Fibers from the iliococcygeus, pubococcygeus and puborectalis muscles fuse to form the levator plate acting as a shelf, which the pelvic organs rest on. When the body is in vertical position, the levator plate thus supports the rectum and upper two thirds of vagina. The muscles contain a majority of type I striated muscle fibers, which maintain a constant resting tone over time. Smaller portions of type II fibers permits the muscle to respond quickly to increases in intra-abdominal pressure.[12]



PPM, puboperineal muscle

PB, perineal body

PAM, puboanal muscle

PRM, puborectalis muscle

ICM, ilicoccygeys muscle

ATLA, tendineous arch

EAS, endoanal sphincter

Figure 1. *The levator ani muscle complex. Reprinted with permission from John DeLancey.*

The endopelvic fascia is a fibromuscular tissue layer surrounding the vagina. It attaches the vaginal walls to the tendinous arch, and coalesces at the vaginal apex to create the cardinal and uterosacral ligaments. The cardinal and uterosacral ligaments pull the vagina toward the sacrum, suspending it over the levator ani muscle plate. The pubocervical fascia has been described as a fibromuscular sheet supporting the anterior compartment, extending from the pubic bone along the anterior vaginal wall to the cervix, and laterally attaching to the tendinous arch. The rectovaginal fascia supports the posterior compartment analogous to the pubocervical fascia in the anterior compartment. The rectovaginal fascia extends from the perineal body, toward the tendinous arch and superiorly fuses with the cardinal and uterosacral ligaments.

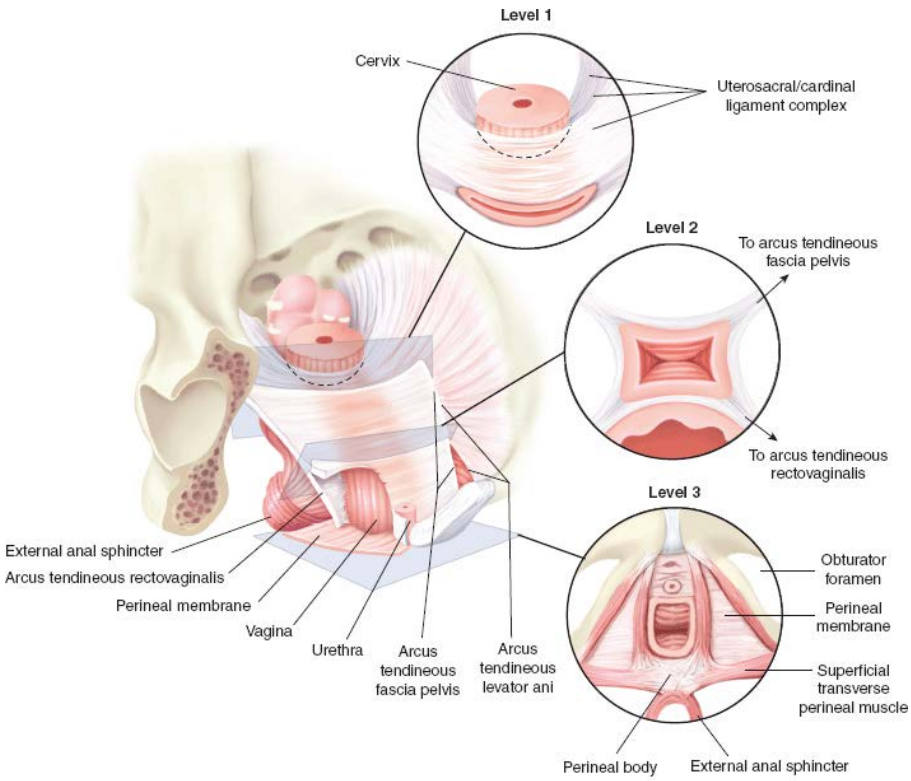


Figure 2. *The endopelvic fascia. Reprinted with permission from Cleveland Clinic Center © 2004.*

2.1.2 The perineal body and the urogenital diaphragm

The perineal body is a soft tissue mass between the vagina and the anorectum, formed by a convergence of the tendinous attachments of multiple pelvic floor muscles.[13] Thin-sliced magnetic resonance imaging (MRI) and cadaver dissection studies has shown that the bulbocavernosus muscle, the superficial and deep transverse perineal muscle, the internal and external anal sphincters as well as the puboperinealis and puboanalis portions of the puborectalis muscle all attach to the perineal body.[14-16] The bulbocavernosus muscles cover the superficial parts of the vestibular bulbs and the major vestibular glands. They consist of striated muscles[15,17] and run from the body of the clitoris, beneath the labia majora surrounding the vaginal orifice, inserting in the upper and lateral part of the perineal body.[18] By contracting they cause a narrowing of the vaginal orifice and by compressing the deep dorsal vein of the clitoris, they contribute to female erection.[19] Some authors have suggested that the perineal body is an important part of the "orgasmic platform".[13]

The superficial transverse perineal muscles run horizontally from the ischial tuberosities, attaching to the central part of the perineum. Together with the deep transverse perineal muscles they fix the perineal body to the bony pelvis and prevent downward descent of the rectum.[19] The posterior part of the perineal body is connected to the external and internal anal sphincter complex. The external anal sphincter is a voluntary, striated, circular muscle that plays a crucial part in anal continence.[20]

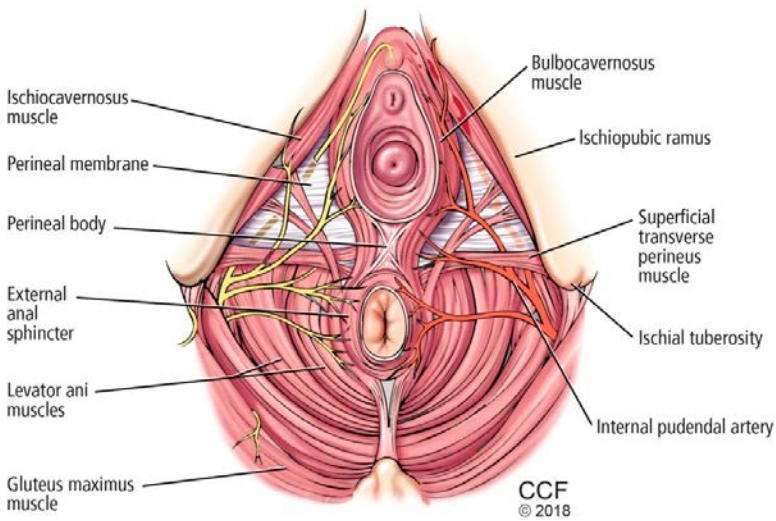


Figure 3. *The female perineal body. Reprinted with permission from Cleveland Clinic Center © 2018.*

If the perineal body becomes injured, the rectovaginal fascia may lose its caudal anchoring point. This results in a distal rectocele, with entrapment of stool in a rectal pouch just behind the sphincter complex. The rectum consequently protrudes into or out of the vaginal orifice during evacuation efforts.[21]

The urogenital diaphragm, located between the superficial perineal body muscles and the levator ani muscles, is a triangle shaped muscle layer created by urethral sphincter muscles and the deep transverse perineal muscles. The urogenital diaphragm is confined among a superior and an inferior layer of fascia. The inferior layer of fascia is often called the perineal membrane. The compressor urethrae inserts anteriorly into the perineal body and the perineal body is thus intimately associated with the levator ani and the urethral sphincter muscles.[14] The integrity of the perineal body is suggested to play a role in maintaining urinary continence.[13]

2.1.3 Levels of support

In 1992 DeLancy described three levels of vaginal support.[22] Level I suspends the upper third of the vagina and is supported by the uterosacral and cardinal ligaments. Level II is the middle third of the vagina and is supported by the endopelvic fascia, including the pubocervical and rectovaginal fascia, and attaches laterally to the tendinous arch. Level III is the most distal portion, which is supported by the levator ani muscles and the perineal body. The perineal body acts as the final mechanism for preventing prolapse beyond the hymen.

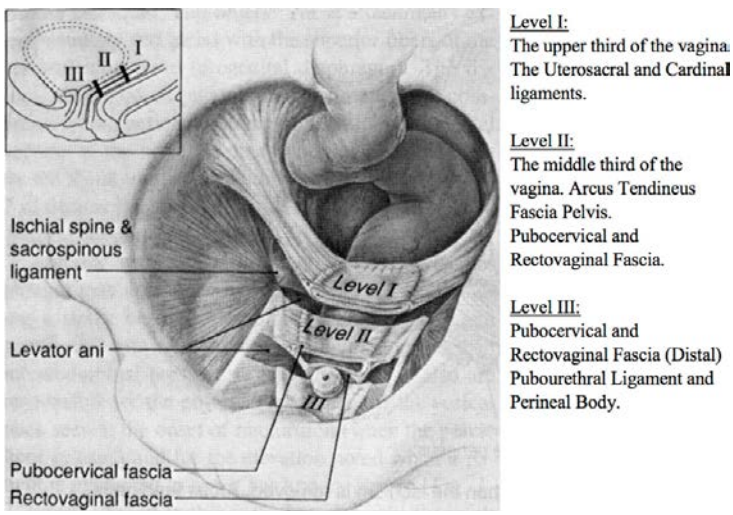


Figure 4. *Levels of support according to Johan DeLancey. Reprinted with permission from the author.*

2.2 PELVIC ORGAN PROLAPSE

2.2.1 Epidemiology and risk factors

POP is defined as the descent of the anterior or posterior vaginal wall, the uterus, or the vaginal vault after hysterectomy. Estimates of the prevalence of POP in a population varies according to the definition of the condition. There is, however, no clear consensus on what level of prolapse represents a variation of normal support and what represents a medical disorder. The following definition of clinically relevant POP has been suggested to reflect both anatomical abnormality and subjective bother: the descent of one or more vaginal compartments beyond the hymen on straining examination associated with feeling or seeing a bulge from the vagina.[23] Where POP is defined based entirely on symptoms (vaginal bulging) the prevalence ranges between 5-10%.[24-27] When using anatomical findings, the prevalence of POP ranges between 30-75% [28-30] with only 3%-10% of women having the leading edge of the prolapse at or beyond the hymen [31,32]. Anterior compartment prolapse is the most frequently reported site of prolapse.[29,33] The lifetime risk of undergoing at least one surgical procedure for POP range from 6-19%.[6,7,34] The etiology of POP is multifactorial and many risk factors have been suggested.[35] Well established risk factors include vaginal childbirth, advancing age, obesity and family history.[1] Increasing number of childbirths seems to increase the risk of POP (figure 5).[1] MRI studies by DeLancey have demonstrated levator ani muscle defects after vaginal childbirth and the same author found an OR of 7.3 for having levator ani defects in women with POP compared to women with normal support.[36,37] In the SWEPOP study by Gyhagen et al, vaginal delivery was associated with a 255% increased risk of POP compared with caesarean section and POP increased 3% with each unit increase of body mass index (BMI).[38] Other risk factors for POP include Caucasian or Hispanic ethnicity, hysterectomy and other pelvic surgery, heavy lifting and chronic constipation.[1]

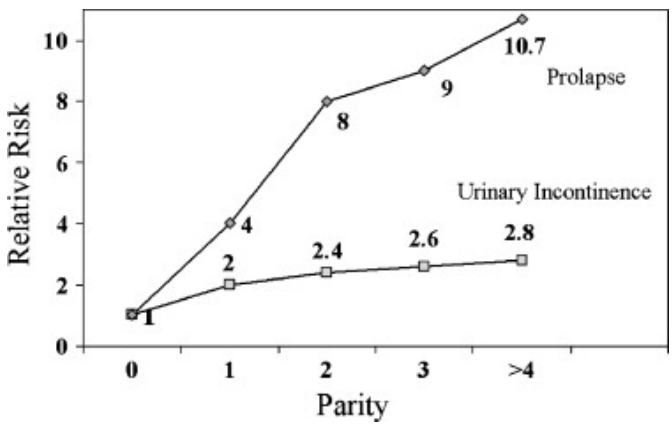


Figure 5. *The relative risk for prolapse and urinary incontinence as a function of the number of vaginal deliveries (adopted from Rotveit and Mant et al) and reprinted with permission from John DeLancey.*

2.2.2 Symptoms and signs

The most specific symptom, which strongly correlates to POP is ”seeing” or ”feeling” a vaginal bulge.[31,39-41] The hymen seems to be an important cut off level regarding presence of symptoms, since women with a prolapse protruding to or below this point are more likely to report vaginal bulging.[30,42] Other mechanical symptoms such as vaginal pressure and heaviness or local discomfort have only weak correlations with objective POP.[41,43] Lower urinary tract symptoms (LUTS), bowel emptying dysfunction, as well as, sexual dysfunction are common among women with POP.[42] However, these symptoms are more unspecific for POP and do not necessarily correlate with compartment-specific defects.[40,43,44] Progressively worsening anterior compartment prolapse lowers the risk of SUI and increases the likelihood of obstructed voiding symptoms due kinking of the urethra.[45] Women undergoing surgical repair of POP have a 9-51% risk of developing de novo SUI postoperatively, which may be a consequence of surgery correcting urethral kinking and thus unmasking incontinence.[46]

From a biomechanical perspective it would be logical that posterior vaginal wall prolapse results in bowel emptying difficulties (straining, splinting and feeling of incomplete emptying). Many studies have, however, failed to demonstrate this relationship [47-50], while other studies do support this association [51-54]. Most studies have not found a dose-response effect, in terms of higher stages of posterior vaginal wall prolapse resulting in increasing symptoms of obstructed defecation.[41,51,52,55] AI share the same risk factors as POP, such as muscular and neuropathic injury caused by vaginal delivery and age. AI may co-exist but is not considered a symptom specific for POP.[39]

Diagnosing and grading the severity of POP involves a clinical gynecological examination with evaluation of the vaginal anatomy. The pelvic organ prolapse quantification system (POP-Q) is an objective tool for describing, quantifying, and staging pelvic support in women.[34] It has been shown to have good intra- and inter-examiner reliability.[56] The position of each compartment is determined at maximum Valsalva, with the patient in a lithotomy position. The hymen is the fixed point of reference defined as point zero. There are six anatomic points in the vagina measured in centimeters above (negative numbers) or beyond (positive numbers) the hymen. An additional three points of measure are registered describing the total vaginal length, genital hiatus and the perineal body. In a multicenter observational study of 1,004 adult women who presented for annual gynecological exam the prevalence of POP-Q stage 0 was 24%, stage I 38%, stage II 35%, and stage III 2% . In total, 75% of women had some degree of POP based on the POP-Q system.[30]

2.2.3 Surgical management

Colporrhaphy is the most common surgical procedure for repair of anterior and posterior vaginal wall prolapse.[57] Colporrhaphy involves a transvaginal incision of the vaginal wall and dissection of the bladder or the rectum from the vaginal mucosa. Fibromuscular tissue in the vaginal sulci are perforated with sutures and adapted in the midline. Finally, excess mucosa is excised and the vaginal mucosa is closed with sutures.

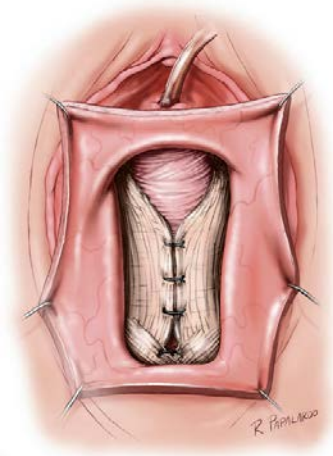


Figure 6. *Anterior colporrhaphy with midline plication. Reprinted with permission from Cleveland Clinic Center © 2002-2013.*

The lack of a standardized definition for treatment success after POP surgery has resulted in highly variable cure rates.[58-60] When strict anatomic criteria (POP-Q stage 0 or I) are used to define success, cure rates of native tissue prolapse repair are as low as 30-64%.[61-63] However, a substantial proportion of women in the general population without symptoms of POP would not meet these criteria.[30] Absence of vaginal bulge symptoms postoperatively strongly correlate with patient's assessment of overall improvement, treatment success, as well as, with improvement in quality of life.[60] When subjective cure or the anatomic criteria "no prolapse beyond hymen" are used to define treatment success, cure rates are considerably better (82%–94%).[63]

The majority of POP recurrences occur within the first year postoperatively, of which anterior vaginal wall prolapse is the most common site for recurrence.[8,64] To address this limitation, biomaterial implants aiming to reinforce native tissue, became increasingly popular in POP surgery during the late 90´s. Reports on long-term side effects related to transvaginal synthetic meshes, such as erosion

and pain, have however turned this trend.[65] Native tissue repair is therefore widely considered the first-line approach in vaginal wall prolapse surgery.[66] Nonetheless, colporrhaphy is far from a standardized procedure.[67] There are very few trials assessing details of the surgical technique used for colporrhaphies and it remains important to identify surgical factors that may optimize the result.

Surgical management of uterine prolapse varies greatly and currently no evidence-based guidelines exist to guide the surgeon when choosing between the different apical suspension procedures.[66] Vaginal hysterectomy has traditionally been the most common approach in the treatment of uterine prolapse [7] but uterus-preserving procedures are now gaining popularity [68,69]. Minimally invasive sacrohysteropexies provide a cure rate of up to 95%.[70] These techniques, however, require both high-technology operating facilities as well as experienced surgeons. Other uterus preserving techniques include sacrospinosus fixation, with or without mesh, and procedures including amputation of the cervix with concurrent vaginal wall plication, also referred to as the Manchester procedure.

2.2.4 The wound healing process and the choice of suture material

The wound-healing process can be divided into three phases, the exudative phase (1–4 days), the proliferative phase (5–20 days), and the remodeling phase (21 days to 2 years).[71,72] The first step in connective tissue repair takes place in the second phase and during this period the tissue regains 15–30% of its original tensile strength. The tissue gains maximum tensile strength during the third phase. The biomechanical properties of most suture materials are described and summarized in a review article by Pillai et al.[73] Tensile strength is a measure of a material or tissue's ability to resist deformation and breakage. Absorbable multifilament sutures such as Vicryl® or Polysorb® have a tensile strength of 75% at 14 days, 50% at 21 days and are totally absorbed within 70 days. The more slowly absorbable monofilament sutures, for example PDS®, withholds more than 50% of its tensile strength for up to 4 weeks and is totally absorbed within 180 days. Another possible benefit of the monofilament sutures is the lower risk of bacterial adherence to the suture material,[74] which could decrease the risk of wound infection, wound dehiscence and delayed healing. Theoretical advantages of a slowly absorbable monofilament suture (for example PDS®) are therefore its delayed absorption, providing support while native tissue is healing, and its presumed lower risk of postoperative infection. The hypothesis that slowly absorbable monofilament sutures would result in better results after prolapse repair compared to the use of absorbable multifilament sutures is, however, sparsely tested in clinical trials.

2.3 URINARY INCONTINENCE

UI is defined as a complaint of any involuntary leakage of urine. SUI is defined as the complaint of involuntary loss of urine on effort or physical exertion, sneezing or coughing in the absence of detrusor contraction. Urgency urinary incontinence (UUI) is defined by involuntary loss of urine associated with urgency (complaint of a sudden, compelling desire to pass urine which is difficult to defer). A combination of these two incontinence types are referred to as mixed urinary incontinence (MUI).

2.3.1 The urinary continence mechanism and pathophysiology of stress urinary incontinence

The female urethral anatomy is described in a review article by Mistry et al.[75] Two smooth muscle layers: an inner longitudinal and an outer thinner circular layer, are present throughout the upper four fifths of the urethra. The smooth muscles are innervated by the autonomous nervous system and are surrounded by striated muscles referred to as the external urethral sphincter, which extends from the bladder neck to the perineal membrane. The external sphincter can be divided into three distinct muscles: *the sphincter urethrae*, which surrounds the proximal two thirds of the urethra, *the compressor* urethrae and *the urethrovaginal* sphincter, both of which originate from the vaginal wall and the ischiopubic ramus and envelope the distal third of the urethra. During rest, submucosal vessels, connective tissue and smooth muscle seal off the lumen. During increased intra-abdominal pressure, for example when coughing or sneezing, adjunctive forces add additional support by activating voluntary muscles of the pelvic floor, such as the external urethral sphincter muscles and parts of the levator ani muscle. Damaged sphincters, support systems (fascia and levator ani muscles) or sensory innervation are all potential causes of UI.

It is widely accepted that SUI may arise as a consequence of two different pathophysiological mechanisms. *Bladder neck hypermobility* or *hypermobility of the urethra* is caused by the lack of mid-urethral support.[76] Paraurethral fascia attaches laterally to the tendinous arch and creates a hammock-like support.[77] The pubourethral ligament, which attach the urethra to the pubic bone, the sub-urethral vaginal hammock and the levator ani muscles all contribute to maintaining urinary continence.[78] The muscles contract and pull the sub-urethral hammock against the pubourethral ligament, thus closing off the urethra.[79] The supporting structures may weaken or become damaged due to vaginal childbirth, obesity or inherent connective tissue weakness. Consequently, the proximal urethra and the bladder neck descend and rotate away and out of the pelvis at times of increased intra-abdominal pressure.[80] Hypermobility is sometimes defined as a downward displacement of the urethra with a maximal straining angle of $\geq 30°$ from baseline. This opens the urethral lumen and small amounts of urine can leak out. Another pathophysiological mechanism that may be a cause of SUI is *intrinsic sphincter deficiency* (ISD), where the urethral sphincter is unable to generate enough pressure to retain urine in the bladder, especially during

increased intra-abdominal pressure.[81] There is no standardized definition for ISD, however, some authors suggest that the diagnosis is made by the finding of a maximal urethral closure pressure < 20 cm H_2O or abdominal leak point pressure of < 60 cm H_2O on urodynamic testing.[82] The urethra in ISD patients usually has little or no mobility and these patients may leak continuously or with minimal exertion. ISD is commonly associated with pelvic surgery, hypoestrogenism and aging.[83]

2.3.2 Epidemiology and risk factors

There is no consensus on an epidemiologic definition of incontinence. Most studies reporting a prevalence of "any UI" have figures ranging between 25% to 45% and for "daily UI" between 5% and 15%.[1] MUI and UUI are the dominating incontinence types in older women, while young and middle-aged women generally report SUI.[1] In a cross-sectional analysis of 1,961 non-pregnant, non-institutionalized US women (≥20 years) by Nygaard et al, where UI was defined as moderate to severe leakage, the prevalence of UI was 16%.[84] The EPINCONT study from 2000 is the largest epidemiological survey carried out on UI to date including 27,936 women.[85] The overall prevalence of urinary incontinence, defined as any leakage, was 25 % showing a clear correlation with increasing age. Furthermore the study showed a peak prevalence in mid-life with a prevalence of 30% among women 50–54 years of age and half of the incontinent women experienced symptoms of SUI alone. The fraction of SUI symptoms was at its highest among women between 25-49 years of age, which means that a considerable number of women with SUI are of childbearing age.

Well established risk factors for urinary incontinence include age, pregnancy and obesity.[1,86] The relative risk of incontinence doubles after the first vaginal delivery as compared to women who are nulliparous and further deliveries may add to the risk.[87] The SWEPOP study demonstrated that the risk of developing UI was 71% higher after one vaginal delivery compared to caesarean section. Other risk factors for UI are family history, diabetes, oral estrogen treatment in women age 55 and older, hysterectomy, physical and cognitive dysfunction and White, non-Hispanic ethnicity.[1]

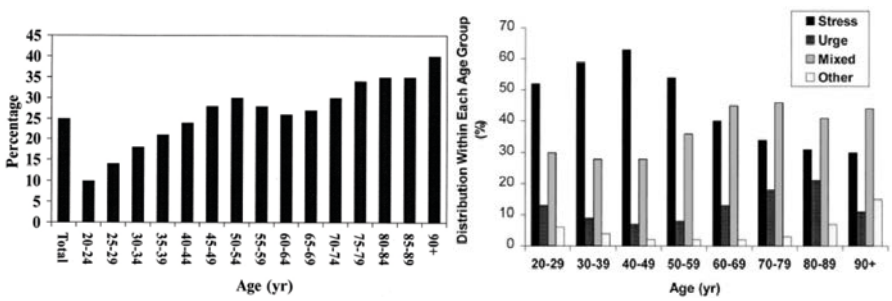


Figure 7. *Prevalence and distribution of types on UI in different age groups (Hunskar et al, Urology, 2003).*

2.3.3 Symptoms and signs

Women affected by UI often restrict their daily and social activities due to fear of unpleasant odor or embarrassing urine loss in public.[88] Patient-reported symptoms, and how these impact daily life, are important both as a primary end-points in determining the severity of UI, and in assessing treatment outcomes.[89] Urinary symptoms can be evaluated in clinical research using validated condition specific questionnaires. The Symptom and Quality of Life Assessment Committee of the International Consultation on Incontinence has performed a detailed review of the literature regarding methods used to diagnose the type and severity of UI.[90] The report includes questionnaires with high levels of psychometric testing, that are recommended for use in research and clinical practice. UI can also be defined by frequency, severity (a combination of frequency and quantity) or by impact (extent of bother or by the degree to which it restricts different activities).

One objective sign of SUI is a so called positive cough stress test.[91] The patient's bladder is filled up to 300 ml and then, in lithotomy position, the patient is asked to perform a series of forceful coughs. The external urethral meatus is observed for urine loss and if this is noted the test is positive. The cough stress test has demonstrated good sensitivity and specificity in the diagnosis of genuine stress incontinence.[92] Pad testing is another non-invasive method for detecting and quantifying severity of urine leakage.[93] The test includes measuring the weight gain of absorbent pads during a test period. Urine loss can be quantified with a fair degree of reliability, but provide no information on the underlying incontinence mechanism.[92] Urodynamics are used to evaluate the pressure-flow relationship between the bladder and the urethra by assessing the filling, storage and voiding phase as well as urethral dynamics. The purpose of urodynamics is to aid in the correct diagnosis of lower urinary tract dysfunction based upon its pathophysiology. Provocative tests can be added aiming to recreate symptoms and assess characteristics of urinary leakage. Urodynamic tests may change clinical decision making but does not seem to result in improved outcomes after treatment.[94]

2.3.4 Surgical treatment

Ulmsten et al. published their initial paper about retropubic tension-free vaginal tape (TVT) in 1996.[95] Given the minimally invasive nature and effectiveness of the procedure, the use of synthetic mid-urethral slings (MUS) has since been broadly adopted and are widely considered as the gold standard procedure for SUI in women, regardless of pathophysiology. [96] The procedure involves introduction of a polypropylene tape (approximately 1 cm in width) beneath the mid-portion of the urethra. The needles are passed either from the vagina through the retropubic route, exiting through a suprapubic incisions, or from the vaginal incision through the obturator membrane exiting true the groin. The sling functions as a backboard

that offers resistance beneath the urethra during increases in intraabdominal pressure, but is tension-free at rest mimicking the pubourethral ligament. The most recent Cochrane review (2017) on MUS operations for SUI concluded that both routes result in similar objective and subjective cure rates in short and medium term.[97] However, results from the four trials assessing reoperation rates after more than five years from the initial MUS procedure favored the retropubic route (RR 8.79, 95% CI 3.4-23.0). The 55 randomized trials included in the Cochrane review showed a pooled subjective cure of 84%. A 17-year, multicenter, observational study of 90 patients showed an objective cure rate of 90% and subjective cure rate of 77%, suggesting that the results are largely sustainable over time.[98] Mid-urethral slings are also effective in treating SUI caused by ISD, however, in these patients the retropubic route seems to result in higher subjective cure rates compared with the trans-obturator route.[99] The synthetic tapes come with a mesh erosion rate of 2%.[97]

Figure 8. *Retropubic and transobturator MUS locations. Reprinted with permission from copyright holder Scott Bodell.*

As an alternative to surgery, non-invasive (conservative) options include pelvic floor muscle training (PFMT), continence devices, and electrical stimulation. Supervised PFMT was compared with MUS as primary treatment of moderate to severe SUI in a multicenter randomized controlled trial of 460 women by Labrie et al.[100] The results from the intention-to-treat analysis showed a subjective success rate of 91% of women in the surgery group and 64% of women in the physiotherapy group. A recent Cochrane review suggest that PFMT should be included as a first-line conservative management program for women with SUI, although sustainability of achieved results at long-term are poorly investigated.[101]

2.3.5 Childbirth after mid-urethral sling surgery

Most physicians recommend delaying UI surgery until childbearing has been completed.[102] Plans for future pregnancies has been regarded as a relative contraindication for SUI surgery.[103] However, the scientific evidence to support this notion, as well as, recommendations to perform an elective caesarean section if pregnancy occurs after a MUS procedure, are based on small case series including sample sizes of 32 to 54 women.[104-107] The rate of SUI in these series have ranged between 70-80% in women having given birth after MUS surgery. None of the studies included a control group (non-exposed women) and the duration of follow-up was limited. Owing to the limited data one may conclude that there is insufficient scientific evidence to guide counseling of women on the safety of childbirth after incontinence procedures.

2.4 PERINEAL BODY INJURIES

2.4.1 Perineal tears

The classification system of perineal injuries created by Abdul Sultan is widely used and adopted by the Royal College of Obstetrics and Gynaecology.[108] According to this classification a first-degree injury involves perineal skin only; a second-degree injury involves the perineal muscles (bulbocavernosus and superficial transverse perineal muscles) but not the anal sphincter; a third-degree injury involves the external sphincter or both the external and internal sphincters; and a fourth-degree injury goes all the way through the anal mucosa.

Although much attention has been paid to the impact of third and fourth degree lacerations, very few studies have evaluated the consequences of a poorly sutured or healed second degree perineal tear. In a qualitative study by Karlström et al, seven women with poorly healed second degree perineal tears after childbirth, eligible for reconstructive surgery (perineorrhaphy), were interviewed.[109] Symptoms reported by the patients were a sensation of a wide/open vagina (and related symptoms such as vaginal flatulence, vaginal soreness, tampons falling out, water entering the vagina when bathing/swimming), a sensation of vaginal heaviness, and bowel emptying difficulties with a need for digital assistance at defecation. Many women reported sexual dysfunction with symptoms such as orgasmic dysfunction and loss of sensation and dyspareunia. To date, there are no published validated questionnaires designed specifically for patients with poorly healed grade two perineal lacerations.

2.4.2 Surgical reconstruction of the perineal body – perineorrhaphy

Perineorrhaphy means suture plication of the perineum and is sometimes used synonymously with perineoplasty (perineal reconstruction). It is performed as either stand-alone surgery or with concomitant vaginal or abdominal POP procedures. However, the indication for performing a perineorrhaphy is not standardized and significant heterogeneity exists in the technique used to perform the procedure.[110] Many clinicians agree that a perineorrhaphy takes place distal to the hymen approximating the bulbocavernosus muscles and the transverse perineal muscles in the midline of the perineum using absorbable sutures. If a repair of the posterior vagina is performed above this point, it is defined as a posterior colporrhaphy.[110] There are very few studies on which to base preoperative counseling of patients regarding benefits and possible adverse effects of secondary reconstructive surgery of the perineum.

Ulubay et al. described anatomical changes, patient satisfaction and sexual function in 38 women undergoing perineorrhaphy.[111] In this study patient satisfaction rate was 88% and a total of four patients (10%) reported de novo dyspareunia postoperatively. Pardo et al. performed vaginal wall repair and perineoplasty in women with the sensation of a wide vagina and reported a patient satisfaction rate of 96% at six months after surgery.[112] Inan et al. studied 40 women undergoing perineoplasty in a Turkish clinic and found that sexual function scores improved significantly.[113] These studies have some major limitations, of which the lack of a control group is the most important drawback. Further, the authors have not used validated instruments for outcome assessments nor have possible changes in different pelvic floor dysfunction symptoms been assessed.

2.5 QUESTIONNAIRES - THEORETICAL ASPECTS

Questionnaires are objective tools to measure subjective phenomena, such as pelvic floor dysfunction symptoms and their impact on quality of life. The validation process means that studies have to be conducted in order to test different aspects, so called psychometric properties, of a questionnaire. Validity refers to the extent to which a questionnaire actually measures what we intend to measure. *Content or face validity* refers to if the questionnaire makes sense to those being measured and to experts in the clinical area, and whether the questionnaire includes important aspects of the condition. *Construct validity* reflects the relationship between the questionnaire and its underlying theories. *Criterion validity* is the degree to which a test measures what it claims to be measuring and can be tested by comparing the results from the questionnaire with “gold standards” of making a diagnosis. *Reliability* is an extent to which the questionnaire produces the same results on

repeated trials. *Test-retest correlation* provides an indication of stability over time. *Internal consistency* concerns the extent to which items within the questionnaire are related to each other. It is also important that questionnaires aiming to assess outcomes can show that they are *responsive* to change in an appropriate way.

The ICS has reviewed all available questionnaires for assessing urinary incontinence and other pelvic floor dysfunction symptoms.[90] Questionnaires were highly recommended and given a grad A if the committee found data supporting that the questionnaire is valid, reliable and responsive to change. Validated questionnaires available in Swedish are: Pelvic Floor Distress Inventory (PFDI), Pelvic Floor Impact Questionnaire (PFIQ), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), Urogenital Distress Inventory (UDI), Urogenital Impact Questionnaire (IIQ) and International Consultation on Incontinence Questionnaires (ICIQ).

3 AIMS OF THE THESIS

The overall aim of this thesis has been to identify variables that could optimize outcomes for women who undergo surgical treatment for symptoms related to pelvic floor dysfunction.

We specifically aimed:

Study I: To investigate if using slowly absorbable monofilament sutures is superior to absorbable multifilament sutures with regard to treatment success after anterior and posterior colporrhaphy.

Study II: To compare patient-reported outcomes, perioperative morbidity and adverse events after cervical amputation versus vaginal hysterectomy in women suffering from uterine prolapse.

Study III: To assess the possible consequences of childbirth on SUI in women who previously underwent mid-urethral sling surgery and to evaluate if symptoms differ with regard to mode of delivery.

Study IV: To compare and evaluate subjective and objective outcomes after perineorrhaphy versus tutored pelvic floor muscle therapy in women with a poorly healed second degree perineal tear.

4 MATERIALS AND METHODS

4.1 SUMMARY OF STUDY DESIGNS

Study I and II are register-based cohort studies based on data retrieved from The Swedish National Register for Gynecological Surgery (GynOp). **Study III** is a cross-sectional survey based study and **Study IV** a randomized controlled study. Table 1 summarizes the study designs according to the PICOT format.[114]

Table 1. *Overview of the studies in this thesis summarized according to the PICOT format*

Study	Study design	Population	Intervention	Comparison	Outcome	Time
I. Does the choice of suture material matter in anterior and posterior colporrhaphy?	Register-based cohort study	Adult women undergoing primary anterior or posterior colporrhaphy	Use of slowly absorbable monofilament suture in the midline plication of the fascia	Use of rapidly absorbable multifilament suture in the midline plication of the fascia	Patient reported sensation of a vaginal bulge	One year
II. Cervical amputation versus vaginal hysterectomy; a population-based register study	Register-based cohort study	Adult women with uterine prolapse	Vaginal hysterectomy ± anterior colporrhaphy	Cervical amputation ± anterior colporrhaphy	Patient reported sensation of a vaginal bulge	One year
III. Associasions between childbirth and urinary incontinence after mid-urethral sling surgery	Population-based cross-sectional study	Adult women with a previous MUS procedure	Childbirth after MUS procedure (both vaginal and cesarean)	No childbirth after MUS procedure	Patient reported stress urinary incontinence	Cross-sectional
IV. Perineorrhaphy compared with pelvic floor muscle therapy in women with late consequences of a poorly healed second-degree perineal tear: a randomized controlled trial	Randomized controlled, open-label trial, with two parallel arms	Adult women with a poorly healed 2nd degree perineal tear minimum 6 months postpartum	Perineorrhaphy with distal posterior colporrhaphy	Tutored pelvic floor muscle therapy	Treatment success defined by the Patient Global Impression of Improvement Scale	Six months

4.2 STUDY I AND II

4.2.1 Data sources

Study I and II are population-based cohort studies based on data retrieved from the Swedish National Quality Register for Gynecological Surgery (GynOp), that prospectively collects information on routine gynecological surgical care in Sweden. The register includes seven sections covering different surgical areas of gynecology (hysterectomies, adnexal procedures, gynecological tumor surgery, hysteroscopy and endometrial ablation, third and fourth degree perineal tears, as well as, POP and SUI surgery). The register was established in 1994 and collection of data regarding POP surgery started in 2006. In 2011 a total of 43 out of 53 (81%) gynecological clinics in Sweden participated in the register. The clinics situated in the county of Stockholm, Värmland and Gotland reported to a different quality register called GKR (Gynekologiskt Kvalitetsregister). In 2012, however, data from the GKR was merged into the GynOp register. Currently a total of 61 clinics report to the register. During 2007 to 2010, the board of the Gynop-register conducted an inspection visit to a total of 15 clinics (both university and county hospitals). They found that the mean proportion of patients included in the register was 96% of all eligible patients. All Swedish national quality registries have so called certification levels of which there are four levels. The levels represents how far the register has reached in terms of analyses, inclusion of relevant variables, coordination with health services, use in research, data quality and reporting, coverage rate, as well as, technical solutions. The GynOp register has the highest possible rating (certification level 1).[115]

Data in the register are collected through patient questionnaires and forms completed by surgeons. The Swedish Urogynaecology Association (UR-Arg) is responsible for part of the content of these forms. The surgical coordination nurse or a secretary at the gynecological department includes the patients and provide them with written information about the register and an option to decline participation. All data extracted from the register for analysis is encoded. Since 2006 patients receives two follow-up questionnaires, one at two months and the other at one year postoperatively.

4.2.2 Study population

Study I includes two separate cohorts. The first cohort (n=1,107) includes adult women with a stage II-III prolapse of the anterior vaginal wall (anterior vaginal wall -1 to + 4 cm in relation to the hymen) having had an isolated anterior colporrhaphy, and no other concomitant procedure, where the surgeon used either rapidly absorbable multifilament sutures (RA sutures) or slowly absorbable monofilament sutures (SA sutures) in the midline plication of the fascia. The second cohort (n=577) includes women with similar inclusion criteria but with a prolapse of the posterior vaginal wall. Exclusion criteria in both cohorts were: previous pelvic floor surgery or hysterectomy; prolapse stages II–IV in another compartment; or a uterus larger than 12 weeks' of gestational age. The operations were performed between September 2012-2013 since registration of suture materials in the register begun in September 2012. Flow chart of the study populations are illustrated in Figure 9-10.

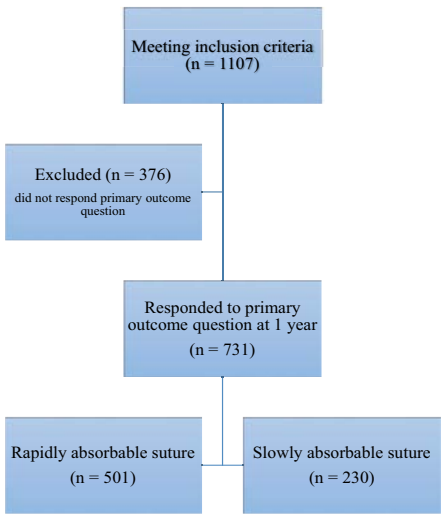


Figure 9. *Flow chart of the anterior colporrhaphy cohort*

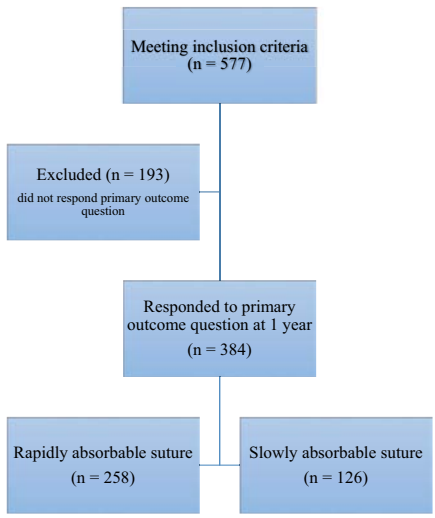


Figure 10. *Flow chart of the posterior colporrhaphy cohort*

Study II consists of 4,047 adult women with uterine prolapse POP-Q stage I–IV having had either cervical amputation or vaginal hysterectomy, with or without concomitant anterior colporrhaphy (figure 11). Exclusion criteria includes previous prolapse or urinary incontinence surgery, a uterus larger than 12 weeks' gestation, and concomitant posterior colporrhaphy.

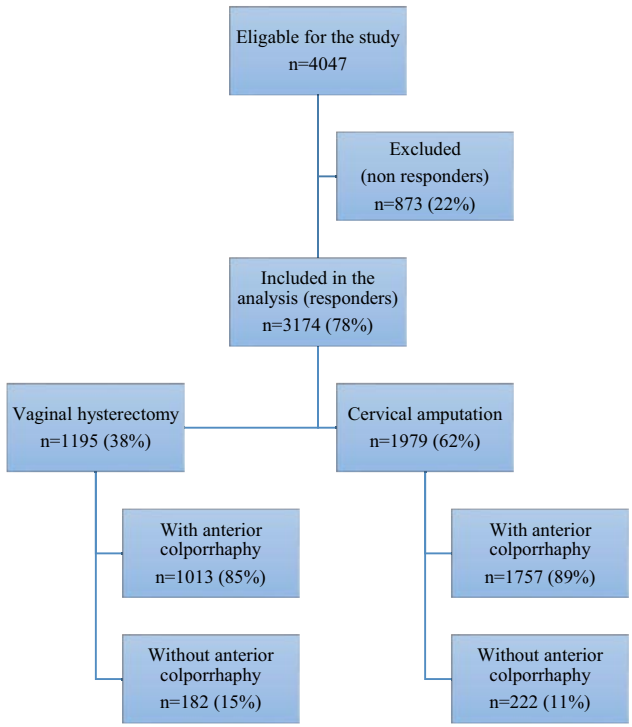


Figure 11. *Flow chart of the study participants in Study II*

4.2.3 Exposures and co-variates

In **Study I** the exposures were two different types of sutures that are used for midline plication of the pubocervical or rectovaginal fascia during a colporrhaphy. Since September 2012 the variable "suture material" has been a part of the mandatory variables recorded by the surgeon. We compared rapidly absorbable multifilament sutures (Vicryl®, Polysorb®) with slowly absorbable monofilament sutures (PDS®, Maxon®). In order to adjust for possible confounding factors two different regression models were used. A model adjusting for age, functional status (ASA class), BMI, parity, menopausal status, and preoperative degree of prolapse resulted in 54% missing subjects, and the sample size was therefore significantly reduced. This model was used as a sensitivity analysis. A model including age (being an important risk factor for POP) and functional status (since there were significant differences in ASA class at baseline) included no missing values and were therefore used as the main analyses. The variables age, preoperative degree of prolapse and ASA class were collected from forms completed by the surgeon, whereas the variables BMI, parity and menopausal status were collected from preoperative questionnaires completed by the patient.

In **Study II** the main exposures were vaginal hysterectomy and cervical amputation performed on prolapse indication. Both procedures were, in the majority of cases, performed with a concomitant anterior colporrhaphy. The regression model adjusted for the following co-variates: age, parity, BMI, preoperative degree of anterior and apical compartment prolapse (according to the POP-Q), concomitant anterior colporrhaphy, bulging symptoms at baseline, and menopausal status.

4.2.4 Outcome measures

The primary outcome in both **Study I and II** was patient-reported vaginal bulging symptoms at the 1-year follow-up questionnaire. The question "Do you experience a feeling of bulging or protrusion in the vaginal area?" was dichotomized from five answer options (never and hardly ever into "no" and 1–3 times per month, 1–3 times per week or daily into "yes"). Secondary outcomes included patient-reported satisfaction, changes in urinary and bowel symptoms and sexual activity. Questions concerning urinary and bowel symptoms were recoded from five answer options into three (never and hardly ever into "never", 1–3 times per month and 1–3 times per week into "sometimes" and daily remained as "daily"). Sexual activity was assessed with the question "Have you had coitus in the past 3 months?" (yes or no). Secondary endpoints also included patient and doctor reported complications.

In **Study II** we manually went through a description of every single doctor or patient reported severe complication in order to specify each severe complication. We categorized them as "severe complications" only if they matched the criteria of a grade 2 complication as defined by the Clavien-Dindo classifications system.[116] In **Study II** we also compared perioperative variables such as operation time, blood loss, days at hospital etc.

4.2.5 Post publication sensitivity analyses of Study I

A study published in 2018 by Bohlin et al. reported on factors influencing outcomes of anterior and posterior vaginal wall prolapse surgery, based on data from the GynOp register.[117] Patients were considered "cured" if they reported vaginal bulging sensation "never", "hardly ever" or "1–3 times per month" at 1 year after surgery (we categorized 1-3 times per month into "non-cured"). Recently published studies have shown that factors associated with prolapse recurrence are: preoperative degree of prolapse,[118,119] levator ani injuries,[119,120] family history,[119,120] age (inverse correlation),[120] BMI,[117,120,121] parity,[118] co-morbidities[118] and preoperative degree of bulging symptoms[117]. We have therefore subsequently tested the robustness of our results by performing additional sensitivity analyses. We performed multivariate logistic regression of the primary outcome in a model adjusting for preoperative degree of prolapse and bulging symptoms, age, BMI, parity and ASA class (as

a proxy for co-morbidities). The analyses are performed with both original data, as well as, with multiple imputation of missing values. We have also tested the robustness of our conclusion by re-categorizing the cutoff for cure versus non-cure as defined by Bohlin et al.

4.3 STUDY III

Study III is a population-based cross-sectional study comparing women with and without childbirth subsequent to MUS surgery.

4.3.1 Data source

In **Study III** we used data from nationwide health care registers supervised by the Swedish Board of Health and Welfare. The Swedish Medical Birth Register was founded in 1973 and includes data on 99% of all deliveries in Sweden. The Patient Register has complete national coverage from 1987 and includes all inpatient care in Sweden. Since 2001 the register also covers outpatient care, including day surgery, from both private and public caregivers. The inpatient register has been validated and has less than 1% yearly missing registrations and correct coding for surgical procedures is achieved in 98% of cases.[122] The missing registration rates in the outpatient register has been reduced from 25-30% during the first year (2001) to only 4% in 2016. The register contains data on individual hospital discharges and surgical procedure codes according to the Swedish Classification of Surgical Procedures. The records also contain dates of admission, discharge, and date of surgery. Using national registration numbers, our exposed and unexposed cohorts (ie, women who had and had not undergone childbirth subsequent to MUS surgery) were linked.

4.3.2 Study population

The study population includes adult women with at least one delivery, either vaginal or cesarean, after a mid-urethral sling procedure (exposed group) and a matched control group including women without any deliveries after their MUS procedure (non-exposed group). The study subjects were identified by linking individual records from the Patient Register with the Medical Birth Register. We identified a total of 207 exposed women, who had undergone a MUS procedure between 2002 and 2014, and had one or more subsequent deliveries. For every woman in the exposed group, we then randomly identified a maximum of three controls (n=521) per case. The women in the control group had no deliveries after their MUS procedure and they were matched to the women in the exposed group by year of surgery and age at surgery. A flow chart of the study population is presented in figure 12.

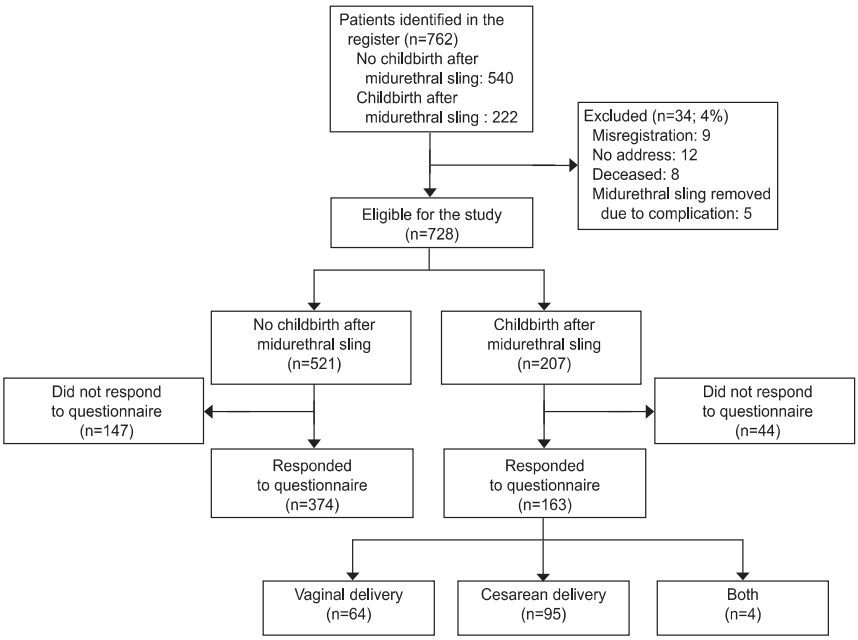


Figure 12. *Flow chart of the study population.*

4.3.3 Exposures and co-variates

The study subjects were defined as exposed if they had a registered retropubic or trans-obturator sling operation (procedure codes LEG 10 and 13) in the Patient Register, and a subsequent delivery (vaginal or cesarean) registered in the Medical Birth Register. The control group was identified using an identical selection process. Matching on age and year at time of surgery was done in order to control for important confounders. In June 2016, questionnaires were mailed to all identified study subjects. In November 2016 a reminder was sent out to non-responders. The questionnaire included UDI and IIQ-7 questionnaires, as well as questions regarding demographic variables (length, current weight, smoking status, parity, mode and year of deliveries, comorbidities, including psychiatric disorders and current medications, previous gynecological procedures, re-operation of a MUS).

4.3.4 Outcome measures

The long version of the UDI and the short version of the IIQ (IIQ-7) were used to assess bother from possible lower urinary tract symptoms and their impact on quality of life. The primary outcome in this study was patient reported SUI. Presence of SUI was defined by patient answering “moderate” or “great” on the question: “Do you experience urine leakage related to physical activity, coughing or sneezing?”

(UDI). No symptoms or only little bother from symptoms were categorized as no SUI. Secondary outcomes included the total UDI score, UDI subscale scores, and IIQ-7 scores. We also tested whether different demographic variables were associated with the primary outcome (presence of bothersome SUI). The exposed group were asked to answer additional questions about if they needed catheterization during the pregnancy after their MUS procedure and if the previous MUS procedure was an indication for cesarean delivery in the subsequent pregnancy.

4.3.5 Urogenital Distress Inventory and Incontinence Impact Questionnaire

UDI is a questionnaire developed in 1994 by Shumaker et al.[123] It includes 19 items and is divided into three subscales reflecting the presence and bother from different aspects of urogenital dysfunction: SUI symptoms, irritative symptoms, and obstructive symptoms. The score from each subscale ranges from 0 to 100, with a maximum summary score of 300. Higher scores indicate greater dysfunction. The IIQ was developed in 1995 by the same research group and includes 30 questions. The IIQ was designed to assess what effect urinary incontinence has on daily activities and emotions in women. A short form consisting of seven items (IIQ-7) has proven to accurately predict the IIQ long-form total score.[124] The score calculated from the IIQ-7 ranges from 0 to 100 with, higher scores indicating greater effect on quality of life. The UDI and IIQ have been shown to significantly correlate with the number of UI episodes and pads used per week.[125] It has been suggested that the UDI-6 (the short form of the 19 item questionnaire) provides predictive results of urodynamic findings.[126] The ICS Committee has given Grade A level of validity to the UDI questionnaire for assessing UI and OAB symptoms.[127]

4.3.6 Power calculation

Previous studies has shown a SUI prevalence of 20 % in women with childbirth after a MUS procedure.[104,106] A Swedish study on long-term outcomes after MUS procedures, without subsequent deliveries, reported a durable cure rate of up to 90 %.[128] A 10 percentage-points difference could be considered clinically relevant. According to these assumptions we needed 133 exposed and 399 unexposed subjects in order to have 80 % power to detect a significant difference between the groups regarding the primary outcome (assuming a 5 % two-sided significance level). Anticipating a non-response rate of at least 15 %, a total of 157 and 470 needed to be invited to participate.

4.4 STUDY IV

Study IV is a randomized controlled, open label trial with two parallel arms comparing surgery and physiotherapy in women with a poorly healed second degree perineal tear.

4.4.1 Setting

The patients included in the trial came on routine internal or external referral to the urogynecological outpatient clinic at the South General Hospital in Stockholm, Sweden. No specific patient advertisement was used. After enrollment, all interventions and follow-ups were carried out at the OBGYN Department at the South General Hospital.

4.4.2 Study population

A total of 70 patients with perineal defects were enrolled in the study. Patients eligible for the study were adult women seeking help due to bothersome pelvic floor dysfunction symptoms and who had a perineal injury (detachment of the bulbocavernosus and/or the transversus perinei muscles), were a perineorrhaphy with distal posterior colporrhaphy was indicated. Other inclusion criteria were; maximal perineal thickness of 2 cm on bidigital palpation, no indication for concomitant pelvic floor surgery, minimum 6 months postpartum and completion of exclusive breastfeeding as well as return of menstruation. Exclusion criteria were; history of a previous forth degree laceration, a connective tissue disorder, current use of systemic corticosteroids, diabetes mellitus, occult sphincter tear on ultrasound or indication for sphincter muscle reconstruction, previous pelvic floor surgery, concomitant pelvic-organ prolapse in the anterior or apical compartment of POP-Q stage 2 or worse.

4.4.3 Randomization and interventions

Eligible patients who consented to participate in the study were randomized in an 1:1 ratio into receiving either surgical repair or conservative treatment. Randomization was performed without stratification in balanced blocks of four, using a web-based tool. All eligibility criteria were checked with an electronic checklist during randomization. The randomization table was designed by an independent statistician.

Patients who were randomized into surgical treatment were scheduled for perineorrhaphy with distal posterior colporrhaphy. The surgical procedure was standardized prior to initiation of the study. The procedures were performed in local anesthesia as day surgery by one of five different pelvic floor surgeons. After informed consent from one of the study participants, the surgical procedure was recorded in order to

illustrate the technique. Patients who were randomized into conservative treatment were referred to one of two different pelvic floor physiotherapists at the OBGYN outpatient clinic at South General Hospital. They received an initial evaluation of the pelvic floor muscle strength and a tutored session with pelvic floor muscle exercises. The patients then received a pelvic floor exercise program to help them build up 10 maximal contractions, each 5 seconds long, three times per day and one maximal contraction 30-60 seconds. They were scheduled for 1-3 follow ups visits depending on the whish from the patient to receive further biofeedback.

4.4.4 Outcome measures

Outcome measures were collected at baseline (initial visit at randomization) and at a 6 months follow-up visit. The primary outcome was treatment success defined as patient choosing answer options “much better” or “very much better” on the Patient Global Impression of Improvement scale (PGI-I) at the 6 months follow-up visit. PGI-I is a seven grade Likert scale where the patient is asked to assess her subjective level of improvement ranging from very much worse up to very much better. Secondary outcomes included comparison of changes in the Pelvic Floor Distress Inventory (PFDI-20), plus three non-validated questions regarding vaginal symptoms, and the Pelvic Floor Impact Questionnaire (PFIQ-7), as well as the Prolapse Incontinence Sexual Questionnaire (PISQ-12) and the Hospital Anxiety and Depression Scale (HAD). Objective outcome measures included an anatomical description of the pelvic floor according to the POP-Q system and evaluation of the perineal body thickness using both ultrasound and bidigital palpation. Surgical characteristics, complications and adverse events during follow-up were registered in a separate protocol.

4.4.5 Power calculation

The current literature does not support a robust formal sample size calculation for the primary outcome of interest. Our power analysis is therefore based on the assumption that 60% in the surgery group and 20% in the physiotherapy group reports subjective cure. According to these assumptions we needed 28 patients in each arm in order to have an 80% power to detect a significant difference between the groups regarding the primary outcome (assuming a 5% two-sided significance level). Anticipating a 20% loss to follow-up a total of 70 (35 in each arm) needed to be recruited.

4.5 STATISTICS

Baseline characteristics of the comparative groups are in all four studies summarized using standard descriptive statistics. Continuous variables are presented as means (± SD) or medians (range or inter-quartile range) and categorical variables as frequencies. For comparison of baseline variables we used the Mann–Whitney U test when analyzing continuous data and Fisher's exact test for categorical variables.

Categorical endpoints in **Study I, II and III** were analyzed using univariate and multivariate logistic regression, dichotomized outcomes with binary regression and multiple answer outcomes with the proportional odds model. Results of the logistic regression analyses are presented as odds ratios with 95 % confidence intervals.

Comparison of outcomes within groups in **Study I, II and IV** were analyzed using the Wilcoxon signed rank test for continuous or ordinal variables and McNemar tests for dichotomized categorical variables.

In **Study IV**, the primary analysis were undertaken on an intention-to-treat (ITT) basis and compared with results of a per protocol analysis. The principal ITT analysis was performed with worst case imputation of missing outcomes (assuming treatment failure). A sensitivity analysis was performed with original data and by imputation of missing data with multiple imputation (10 iterations). An as-treated approach was used when assessing perioperative data and safety. Effect sizes (odds ratios with 95% confidence intervals) of the primary outcome were calculated using univariate logistic regression. Categorical endpoints were compared with Fishers exact test and continuous outcomes are analyzed using the Mann–Whitney U test.

A p value of <0.05 was considered significant for all comparisons. Statistical analyses were performed using SPSS version 22 and 23 software (IBM, Armonk, NY, USA). All statistical analyses and models were designed and conducted in cooperation with one of the three biostatisticians at our institution.

5 RESULTS

5.1 STUDY I

5.1.1 Patient characteristics

The response rate to the primary outcome question at one year postoperatively was 66% in both cohorts. There was no difference in baseline characteristics between responders and non-responders (data not shown). The RA suture group included women undergoing colporrhaphy, where the surgeon used either Vicryl® (n=351) or Polysorb® (n=150) and the SA suture group included the sutures PDS® (n=225) and Maxon® (n=5). Baseline characteristics of the study population in the anterior colporrhaphy cohort are presented in Table 2 and of the posterior colporrhaphy cohort in Table 3. In both cohorts, the two suture groups were similar regarding all variables except for functional status (ASA class). The SA suture group in both cohorts had relatively more patients with higher ASA classes.

Table 2. *Baseline characteristics of the 731 study participants in the anterior colporrhaphy cohort*

Characteristics	RA suture ($n=501$)	SA suture ($n=230$)	p value
Age at surgery (years) mean (±SD)[a]	65.3 (±10.6)	67.2 (±10.7)	0.54
Body mass index (kg/m^2) mean (±SD)[b]	25.7 (±3.6)	26.0 (±3.5)	0.46
Parity median (range)[c]	2 (0–7)	2 (0–8)	1.0
Cesarean deliveries, *n* (%)			
Yes	9 (7)	5 (5)	0.78
No	126 (93)	93 (95)	
Current smokers, *n* (%)			
Yes	24 (11)	9 (6)	0.10
No	188 (89)	143 (94)	
Estrogen replacement therapy, *n* (%)			
Yes	10 (5)	9 (6)	0.64
No	207 (95)	149 (94)	
Postmenopausal, *n* (%)			
Yes	176 (86)	134 (88)	0.75
No	28 (14)	19 (12)	
Functional status (ASA class), *n* (%)			
I	266 (53)	97 (42)	0.01
II	216 (43)	107 (51)	
III	19 (4)	16 (7)	
POP-Q stage anterior wall, *n* (%)			
II	349 (70)	155 (67)	0.55
III	152 (30)	75 (33)	

[a] Analysis includes a total of 731 patients

[b] Analysis includes a total of 561 patients

[c] Analysis includes a total of 570 patients

Table 3. *Baseline characteristics of the 384 study participants in the posterior colporrhaphy cohort*

Characteristics	RA suture ($n=258$)	SA suture ($n=126$)	p value
Age at surgery (years) mean (±SD)[a]	58.8 (±12.6)	59.3 (±14.1)	0.73
Body mass index (kg/m^2) mean (±SD)[b]	26.8 (±4.9)	26.6 (±4.4)	0.75
Parity median (range)[c]	2 (1–7)	3 (0–9)	0.07
Cesarean deliveries, *n* (%)			
Yes	15 (9)	9 (10)	0.82
No	154 (91)	78 (90)	
Current smokers, *n* (%)			
Yes	16 (17)	10 (11)	0.30
No	79 (83)	79 (89)	
Estrogen replacement therapy, *n* (%)			
Yes	8 (8)	8 (9)	1.0
No	88 (92)	83 (91)	
Postmenopausal, *n* (%)			
Yes	66 (70)	63 (72)	0.87
No	28 (30)	24 (28)	
Functional status (ASA class), *n* (%)			
I	138 (53)	56 (44)	0.002
II	113 (43)	56 (44)	
III	6 (2)	14 (12)	
POP-Q stage posterior wall, *n* (%)			
II	184 (71)	93 (74)	0.63
III	152 (29)	33 (26)	

[a] Analysis includes a total of 384 patients

[b] Analysis includes a total of 267 patients

[c] Analysis includes a total of 272 patients

5.1.2 Outcomes

There were no significant differences in pelvic floor dysfunction symptoms at baseline between the groups. The SA suture group had a significantly lower rate of vaginal bulging symptoms (primary outcome) at one year postoperatively compared to the RA suture group; 50/230 (22 %) versus 152/501 (30 %), adjusted OR 1.6, 95% CI 1.1-2.3, p = 0.01. Patient-reported satisfaction was also better in the SA suture group, 83% were satisfied with the result compared with 75% in the RA suture group (p = 0.03). Improvement of both bladder and bowel symptoms occurred within both groups. Urinary urgency improved significantly more in the RA suture group (p<0.001). There were no differences between the two suture groups regarding all other bladder and bowel symptoms.

In the **posterior colporrhaphy cohort** there was no significant difference between the two suture groups regarding the primary outcome, vaginal bulging, at one year after surgery. Vaginal bulging was reported by 21% in the SA suture group and by 20% in the RA suture group (p=1.0). There was no difference in patient reported satisfaction or any of the pelvic floor dysfunction symptoms. There were no significant differences in complications reported by the patient or the surgeon, neither in the anterior nor in the posterior colporrhaphy cohort.

5.1.3 Post publication sensitivity analyses of Study I

We have tested the robustness of our conclusions in the anterior colporrhaphy cohort by performing a multivariate regression model adjusting for co-variates that have been reported to increase the risk of recurrence; age, parity, BMI (in WHO categories <25, 25-29, >30), ASA class (as a proxy for co-morbidities), preoperative degree of prolapse and bulging symptoms. The adjusted OR with original data, which included 26% missing cases, was 1.6 (95% CI 1.04-2.7), p=0.035. The adjusted OR with imputed data (multiple imputation with 10 iterations) was 1.8 (95% CI 1.2-2.7), p=0.008. Changing the cut-off for cure according to the definition by Bohlin et al[117] resulted in 85% cured in the SA group and 75% cured in the RA group. A comparison between the suture groups using the new cut off and the above described regression model did not alter the results.

5.2 STUDY II

5.2.1 Patient characteristics

Baseline characteristics of the final study population available for analysis (n=3,174) are presented in Table 4. A greater number of women in the cervical amputation group were postmenopausal and concomitant anterior colporrhaphy was somewhat more common in the cervical amputation group. The vaginal hysterectomy group had higher POP-Q stages of the apex and the anterior wall at baseline (figure 13).

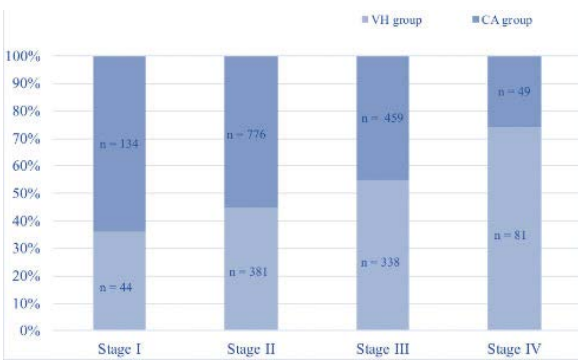


Figure 13. *Vaginal hysterectomies in relation to cervical amputations at different stages of uterine prolapse.*

Table 4. *Baseline characteristics of the study population (n=3174)*

Characteristics	VH group (n = 1195)	CA group (n = 1979)	p-value
Age at surgery (yr) mean (±SD)	63.2 (± 10.4)	63.1 (± 10.5)	1.0
Body mass index (kg/m²) mean (±SD)	25.9 (± 4.1)	25.8 (± 3.8)	0.6
Parity median (range)	2 (0-10)	2 (0-10)	0.1
Cesarean sections median (range)	0 (0-3)	0 (0-3)	0.4
Current smoker n (%)			
Yes	118 (11)	158 (10)	0.3
No	960 (89)	1461 (90)	
Estrogen replacement therapy n (%)			
Yes	67 (6)	87 (5)	0.4
No	1049 (94)	1591 (95)	
Postmenopausal n (%)			
Yes	800 (77)	1284 (81)	0.03
No	236 (23)	307 (19)	
Functional status (ASA class) n (%)			
I	699 (58)	1203 (61)	0.5
II	464 (39)	731 (37)	
III	32 (3)	44 (2)	
POP-Q stage apex n (%)			
I	44 (5)	134 (9)	
II	381 (45)	776 (55)	<0.001
III	338 (40)	459 (32)	
IV	81 (10)	49 (4)	
POP-Q stage anterior wall n (%)			
I	38 (5)	89 (6)	<0.001
II	351 (43)	716 (52)	
III	359 (44)	536 (39)	
IV	75 (9)	47 (3)	
Concomitant anterior colporrhaphy n (%)			
Yes	1013 (85)	1757 (89)	0.001
No	181 (15)	222 (11)	

5.2.2 Outcomes

Both groups improved significantly regarding all pelvic floor dysfunction symptoms and also became more sexually active (Table 5). A comparison of symptom improvement and patient satisfaction at one year are presented in Table 6. A total of 81% in both groups reported absence of vaginal bulging at follow-up. There were no significant differences in patient satisfaction rates (89% vs. 89%). An analysis of the primary outcome i.e. vaginal bulging at one year, stratified by stage of prolapse, showed no differences between the groups. Variables associated with the primary

outcome were age and BMI. Patients with vaginal bulging postoperatively were somewhat younger (mean age ± SD; 61.5 ± 10.5 vs 63.4 ± 10.3, p = 0.001) and had a higher BMI (mean BMI ± SD; 26.2 ± 4.3 vs 25.7 ± 3.8, p = 0.04). When women reporting vaginal bulging 1-3 times per month at follow-up were re-categorized into "no vaginal bulging", the cure rates were 86% in the cervical amputation group and 87% in the vaginal hysterectomy group (aOR 1.2, 95% CI 0.9-1.7).

Table 5. *Comparison of patient reported symptoms within groups. Figures are numbers (%).*

Symptoms	**VH group** (n = 1195)			**CA group** (n = 1979)		
	Preop	Postop	p-value	Preop	Postop	p-value
Vaginal bulging						
yes	1017 (94)	223 (19)	<0.001	1686 (96)	336 (19)	<0.001
no	62 (6)	972 (81)		73 (4)	1613 (81)	
Satisfaction						
Satisfied		1028 (89)			1714 (89)	
Neither nor		90 (8)			134 (7)	
Dissatisfied		37 (3)			69 (4)	
Straining to void						
Never	545 (51)	999 (86)	<0.001	917 (53)	1636 (85)	<0.001
Sometimes	171 (16)	89 (8)		307 (18)	179 (9)	
Daily	344 (33)	71 (6)		509 (29)	117 (6)	
Urinary incontinence						
Never	649 (60)	892 (76)	<0.001	1069 (61)	1443 (74)	<0.001
Sometimes	265 (25)	188 (16)		452 (26)	365 (19)	
Daily	165 (15)	97 (8)		241 (14)	143 (7)	
Urgency						
Never	331 (29)	764 (66)	<0.001	571 (33)	1267 (67)	<0.001
Sometimes	302 (28)	249 (22)		534 (31)	432 (23)	
Daily	469 (43)	144 (12)		640 (38)	193 (10)	
Nocturia						
0-1 times per night	817 (74)	975 (82)	<0.001	1337 (75)	1607 (81)	<0.001
≥ 2 times per night	288 (26)	217 (18)		448 (25)	366 (19)	
Straining to defecate						
Never	744 (69)	927 (79)	<0.001	1230 (71)	1504 (78)	<0.001
Sometimes	246 (23)	203 (17)		408 (23)	345 (18)	
Daily	83 (8)	44 (4)		107 (6)	75 (4)	
Digitation						
Never	861 (82)	1035 (90)	<0.001	1436 (84)	1728 (90)	<0.001
Sometimes	131 (12)	95 (8)		200 (12)	147 (8)	
Daily	63 (6)	28 (2)		72 (4)	34 (2)	
Sexually active						
No	632 (59)	577 (52)	<0.001	1042 (59)	986 (53)	<0.001
Yes	448 (41)	534 (48)		715 (41)	879 (47)	

Table 6. *Comparison of patient reported postoperative symptoms between groups. Figures are numbers (%).*

Symptoms	**VH group**[a] (n = 1195)	**CA group** (n = 1979)		
	Postop	Postop	OR (95% CI)[b c],	p-value
Vaginal bulging				
Yes	223 (19)	336 (19)	1.0 (0.7-1.3)	0.8
No	972 (81)	1613 (81)		
Satisfaction				
Satisfied	1028 (89)	1714 (89)	1.1 (0.8-1.5)	0.6
Neither nor	90 (8)	134 (7)		
Dissatisfied	37 (3)	69 (4)		
Straining to void				
Never	999 (86)	1636 (85)	0.8 (0.6-1.1)	0.2
Sometimes	89 (8)	179 (9)		
Daily	71 (6)	117 (6)		
Urinary incontinence				
Never	892 (76)	1443 (74)	1.0 (0.8-1.3)	0.9
Sometimes	188 (16)	365 (19)		
Daily	97 (8)	143 (7)		
Urgency				
Never	764 (66)	1267 (67)	0.9 (0.8-1.2)	0.6
Sometimes	249 (22)	432 (23)		
Daily	144 (12)	193 (10)		
Nocturia				
0-1 times per night	975 (82)	1607 (81)	0.9 (0.6-1.2)	0.4
≥ 2 times per night	217 (18)	366 (19)		
Straining to defecate				
Never	927 (79)	1504 (78)	1.1 (0.8-1.3)	1.0
Sometimes	203 (17)	345 (18)		
Daily	44 (4)	75 (4)		
Digitation				
Never	1035 (90)	1728 (90)	1.1 (0.9-1.5)	0.3
Sometimes	95 (8)	147 (8)		
Daily	28 (2)	34 (2)		
Sexually active				
No	577 (52)	986 (53)	1.0 (0.8-1.4)	0.8
Yes	534 (48)	879 (47)		

[a] reference
[b] modulated towards negative values
[c] adjusted for age, parity, body mass index (BMI), degree of anterior and apical compartment prolapse, concomitant anterior colporrhaphy, symptoms at baseline and menopausal status.

5.2.3 Adverse events

Severe complications were more common in the hysterectomy group as compared to the cervical amputation group, 23/1,195 (1.9 %) versus 4/1,979 (0.2 %), $p < 0.001$. Severe complications in the hysterectomy group were: intra-abdominal bleeding (n = 8), severe intra-abdominal infection or sepsis (n = 7), ureteric injuries (n = 4), bowel injuries (n = 2), myocardial infarction (n = 1), and severe complications related to anesthesia (n = 1). Severe complications in the cervical amputation group consisted of: severe bleeding (n= 2) and severe infection (n = 2). The rate of doctor reported mild to moderate complications were similar between the groups, 146 out of 1,195 (12.2 %) in the vaginal hysterectomy group versus 246 out of 1,979 (12.4 %) in the cervical amputation group, $p = 0.9$.

The hysterectomy group had a significantly longer mean duration of surgery (76.2 vs 50.0 min, $p < 0.001$), greater mean amount of blood loss (100.1 vs 44.6 ml, $p < 0.001$) and received prophylactic antibiotics as well as prophylaxis against venous thrombosis to a greater extent. The hysterectomy group had also a longer hospitalization (1.7 vs 0.8 days, $p < 0.001$) and a longer period until return to normal activities of daily living (6.1 vs 4.8 days, $p < 0.001$).

5.3 STUDY III

5.3.1 Patient characteristics

A total of 163 women with childbirth after mid-urethral sling surgery and 374 women in the control group were included in the final analysis. A sensitivity analysis investigating characteristics of non-responders showed no significant differences regarding age, concomitant prolapse surgery and number of years postoperatively and postpartum. A total of 86% of the women in the study group had one delivery, 13% had two deliveries, and 1% had three deliveries after their mid-urethral sling procedure. Demographic characteristics are presented in Table 7. There were no differences between the groups except for number of years postpartum and total parity. When comparing women with vaginal and cesarean delivery after a mid-urethral sling procedure, the groups were also similar regarding demographic characteristics except for parity and smoking status.

Table 7. *Baseline characteristics of the study population*

Characteristic	All Participants: Childbirth After MUS Surgery (n=163)	All Participants: No Childbirth After MUS Surgery (n=374)	P	Childbirth After MUS Surgery: Vaginal Delivery After MUS Surgery (n=64)	Childbirth After MUS Surgery: Cesarean Delivery After MUS Surgery (n=95)	P
Age (y)	42 (28–56)	43 (28–57)	.63	43 (34–56)	43 (28–55)	.49
Years after primary MUS surgery	9 (2–14)	8 (2–15)	.98	9 (3–14)	8 (2–14)	.60
Years postpartum	6 (2–19)	13 (4–31)	<.001	6 (2–19)	6 (2–13)	.86
BMI (kg/m^2) 30 or greater	19 (12)	49 (13)	.78	12 (19)	7 (8)	.05
Parity	3 (1–7)	2 (1–5)	<.001	3 (1–7)	3 (1–6)	.02
Mode of delivery						
Vaginal	2 (0–6)	2 (0–5)	.32	3 (1–6)	2 (0–4)	<.001
Cesarean delivery	1 (0–4)	0 (0–3)	<.001	0 (0–1)	1 (1–4)	<.001
Smokers	12 (7.5)	33 (9)	.74	9 (14)	3 (3)	.02
Postmenopausal	13 (8)	46 (12)	.18	6 (9)	7 (7)	.77
Comorbidity	59 (36)	129 (35)	.69	28 (44)	30 (32)	.14
Psychiatric disorder	23 (14)	53 (14)	1.0	11 (17)	12 (13)	.49
Use of anticholinergic drug	4 (2.5)	5 (1)	.46	1 (2)	2 (2)	1.0
Concomitant prolapse surgery during primary MUS surgery	5 (3)	18 (5)	.49	0 (0)	5 (5)	.08
Any previous prolapse surgery	14 (9)	21 (6)	.25	4 (6)	10 (11)	.40
Hysterectomy	6 (4)	24 (6.5)	.31	2 (3)	4 (4)	1.0
Reoperation of MUS surgery	20 (12)	28 (7.5)	.07	11 (17.5)	9 (10)	.22

MUS, midurethral sling; BMI, body mass index.
Data are median (range) or n (%) unless otherwise specified.
Mann–Whitney *U* test was used when analyzing continuous data; Fisher exact test was used for categorical variables.

5.3.2 Outcomes

Patient-reported SUI was equally common among women with and without childbirth after a MUS procedure: 22% of women with a delivery after a MUS procedure reported moderately to greatly bothersome SUI in comparison to 17% in the control group (aOR 1.2, 95 % CI 0.7-2.0). When we changed the cutoff for SUI to include also mildly bothersome symptoms, a total of 48% of the women in the exposed group reported SUI compared with 45% in the unexposed group (aOR 1.0, 95% CI 0.6–1.5). Vaginal delivery in comparison to cesarean section after a MUS procedure did not increase the prevalence of SUI. A total of 22% in both groups reported SUI (aOR 0.6, 95% CI 0.2–1.4). Variables associated with the presence of SUI symptoms were obesity (BMI 30 or greater), psychiatric disorder, history of a secondary MUS or POP procedure (Table 8). The overall subjective success rate in women with a repeat sling procedure was 68%. We found no significant difference in patient reported SUI rates when comparing women with one delivery (n=140) versus more than one deliveries (n=22) after their MUS procedure, 79% versus 73% (aOR 1.2, 95% CI 0.3-4.7) or when comparing women with multiple deliveries after their MUS with the control group, 83% versus 73% (aOR 0.8, 95% CI 0.2-2.5).

Table 8. *Univariate and multivariate regression analysis of clinical co-variates associated with SUI.*

	SUI*, n (%)	**No SUI,** n (%)	**cOR** (95% CI)	**aOR** (95% CI)	**P value**
Childbirth after MUS surgery					
Yes	36 (22)	127 (78)	1.4 (0.9-2.2)	1.2 (0.7-2.0)	0.50
No	63 (17)	308 (83)	Ref	Ref	
Body Mass Index, kg/m²					
< 30	76 (17)	383 (83)	Ref	Ref	
≥ 30	23 (34)	45 (66)	2.6 (1.5-4.5)	2.7 (1.5-4.5)	0.001
Parity					
1-2	48 (15)	263 (85)	Ref	Ref	
≥ 3	51 (23)	170 (77)	1.6 (1.1-2.5)	1.4 (0.9-2.3)	0.17
Smoker					
Yes	7 (16)	38 (84)	Ref	Ref	
No	92 (19)	394 (81)	1.3 (0.5-2.9)	1.5 (0.6-3.6)	0.38
Postmenopausal					
Yes	11 (19)	48 (81)	Ref	Ref	
No	88 (19)	384 (81)	1.0 (0.5-2.0)	1.0 (0.5-2.1)	0.94
Co-morbidity					
Yes	39 (21)	148 (79)	1.3 (0.8-2.0)	1.2 (0.7-2.2)	0.54
No	60 (17)	286 (83)	Ref	Ref	
Psychiatric disorder					
Yes	22 (29)	54 (71)	2.0 (1.2-3.5)	2.2 (1.1-4.7)	0.04
No	77 (17)	380 (83)	Ref	Ref	
Reoperation of MUS					
Yes	15 (32)	32 (68)	2.2 (1.2-4.3)	2.3 (1.2-4.6)	0.02
No	84 (17)	401 (83)	Ref	Ref	
Previous other prolapse surgery					
Yes	12 (34)	23 (66)	2.5 (1.2-5.1)	2.6 (1.2-5.6)	0.02
No	87 (17)	410 (83)	Ref	Ref	
Hysterectomy					
Yes	4 (13)	26 (87)	0.7 (0.2-1.9)	0.6 (0.2-1.9)	0.36
No	95 (19)	406 (81)	Ref	Ref	

* SUI, stress urinary incontinence

A total of 3/163 women (1.8%) reported a need for bladder catheterization during pregnancy subsequent to a MUS procedure. 73 of 95 (77%) women delivered by cesarean section after their MUS procedure reported the sling procedure being the indication for cesarean delivery.

There were no differences in UDI and IIQ-7 scores between any of the groups (Table 9). Figure 14 illustrates a visual comparison of the UDI domain scores and IIQ-7 scores in box plots, displaying medians, interquartile ranges, and outliers.

Table 9. *Comparison of Scores From the Urinary Distress Inventory and the Short Form of the Incontinence Impact Questionnaire*

	All participants			Childbirth after MUS surgery		
Outcome measure	**Childbirth after MUS surgery n=163**	**No childbirth after MUS surgery n=373**	**p value**	**Vaginal birth after MUS n=64**	**Cesarean section after MUS n=95**	**p value**
Total UDI *	57±55	52±52	0.33	59±57	55±53	0.74
UDI-S †	22±26	20±26	0.26	24±28	20±25	0.40
UDI-I ‡	22±22	20±20	0.60	22±24	22±21	0.72
UDI-O §	13±15	12±15	0.22	13±14	13±16	0.78
IIQ-7 ||	11±19	10±19	0.41	10±19	11±20	0.70

* Reflects presence and bother from different aspects of urogenital dysfunction, higher scores indicate greater dysfunction. Ranges from 0-300.

† Reflects stress incontinence symptoms. Ranges from 0-100.

‡ Reflects irritative urinary symptoms. Ranges from 0-100.

§ Reflects obstructive micturition and prolapse symptoms. Ranges from 0-100.

|| Reflects impact of urinary symptoms on quality of life. Ranges from 0-100.

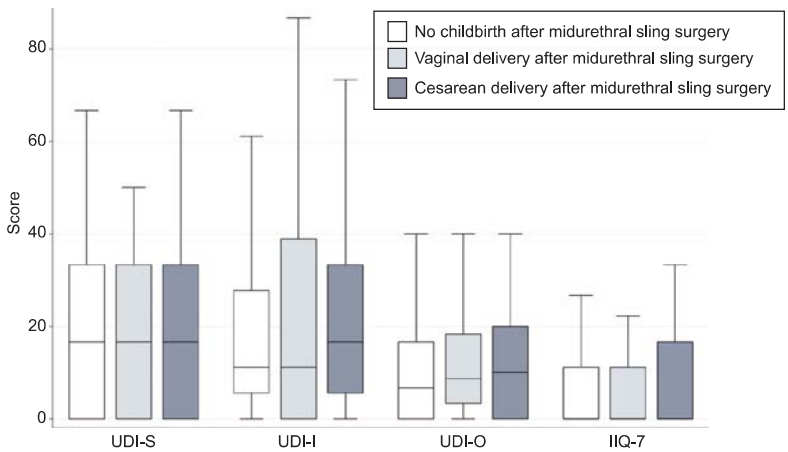


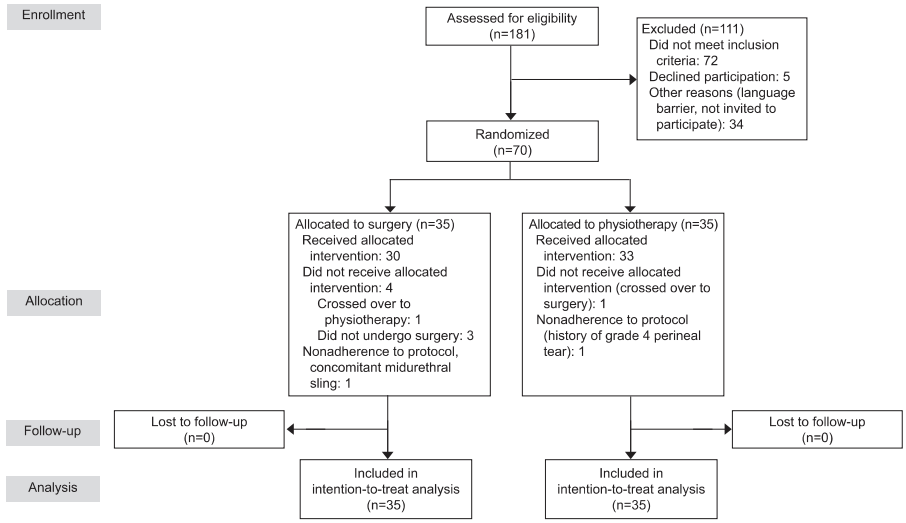
Figure 14. *Comparison of Urinary Distress Inventory (UDI) domains and Incontinence Impact Questionnaire (short form) (IIQ-7) scores (0–100) between the groups. UDI-S, stress urinary incontinence symptoms; UDI-I, irritative symptoms; UDI-O, obstructive symptoms.*

5.4 STUDY IV

5.4.1 Patient characteristics

A total of 109 women fulfilled the eligibility criteria during the enrollment period. 70 women gave informed, written consent to participate in the study. Figure 15 illustrates a flow chart of the patients according to the CONSORT guidelines. Table 10 demonstrates the baseline characteristics of the study population. There were no differences in baseline characteristics when comparing the two treatment groups.

Figure 15. *The flow of patients through the trial according to the criteria recommended in the CONSORT Guidelines.*



Guidelines.

Table 10. *Baseline characteristics of the study population*

Characteristics	**Surgery group** n=35	**Physiotherapy group** n=35
Age (y)	36 (6)	33 (7)
Parity	2 (1)	2 (0)
Mode of delivery		
Vaginal	2 (1)	2 (1)
Cesarean section	0 (0)	0 (0)
Months postpartum	12 (37)	9 (30)
BMI (kg/m2)	23 (5)	22 (5)
Current smoker, n (%)	3 (9)	3 (9)
Maximal degree of tear during any delivery, n (%)		
2nd	28 (80)	30 (86)
3rd	7 (20)	5 (14)
Hormonal contraception, n (%)	5 (14)	7 (20)
PFDI score*	80 (74)	94 (89)
PFIQ-7 score*	48 (76)	52 (57)
PISQ score*	33 (11)	32 (7)
HAD score*	10 (9)	12 (9)
Perineal body height on bidigital palpation, n (%)		
<1cm	15 (43)	9 (26)
1-2 cm	20 (57)	26 (74)
Perineal body height on 2D ultrasound (mm)	8 (3)	8 (3)
Genital hiatus (gh) (cm)	4 (0.7)	3.5 (1)
Anterior vaginal wall (Ba) (cm)	- 2 (1)	- 2 (1)
Posterior vaginal wall (Bp) (cm)	- 2 (2)	- 2 (3)
Cervix (c) (cm)	- 7 (1)	- 6 (2)
Total vaginal length (tvl) (cm)	9 (1)	8 (2)

BMI, Body mass index. Calculated by dividing weight in kilograms by height in meters squared.

PFDI, Pelvic floor distress inventory. Scores ranges from 0-300.

PFIQ Short form of pelvic floor impact questionnaire. Scores ranges from 0-300.

PISQ, Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire. Scores ranges from 0-48.

HAD, Hospital anxiety and depression scale. Scores ranges from 0-21.

Data are median (interquartile range) or n (%) unless otherwise specified.

Mann–Whitney U test was used when analyzing continuous data; Fisher exact test was used for categorical variables.

There were no statistically significant ($p < 0.05$) differences between the groups at baseline.

5.4.2 Outcomes

In the intention-to-treat analysis with worst case imputation, treatment success, defined as answer options “much better” and “very much better” on the Patient Global Impression of Improvement scale, was significantly more frequent in the surgery group, 25/35 (71%) versus 4/35 (11%), p<0.001. The result of the per-protocol analysis was similar (Table 11).

Table 11. *Primary outcome in the surgery group and physiotherapy group at 6 months*

	Surgery group	Physiotherapy group	Treatment effect (95% CI) percentage points	OR (95% CI)
PGI-I – Intention to treat -analysis with worst case imputation	n=35	n=35		
Treatment success	25 (71)	4 (11)	60.0 (41.7-78.3)	19 (5-69)
PGI-I – Intention to treat -analysis with multiple imputation	n=35	n=35		
Treatment success	27 (77)	4 (11)	65.7 (48.3-83.2)	29 (8-112)
PGI-I – Intention to treat -analysis without imputation	n=32	n=35		
Treatment success	25 (78)	4 (11)	66.7 (48.9-84.5)	27 (7-105)
PGI-I – Per Protocol analysis	n=30	n=33		
Treatment success	24 (80)	3 (9)	70.9 (53.6-88.3)	46 (11-203)

PGI, Patient global impression of improvement. Treatment success is defined as patient choosing answer options “much better” or “very much better”.

OR, odds ratio; CI, Confidence Interval

Effect sizes in odds ratios with 95% confidence intervals are calculated with univariate logistic regression.

Table 12 presents the secondary outcomes within both groups at baseline and at the 6 month follow-up visit. All questionnaire scores (including every subscale) among the patients receiving surgical treatment improved significantly. The physiotherapy group improved only in the prolapse domain of the PFDI and in the PISQ-12 scores (sexual function).

Table 12. *Within-group comparison of secondary outcomes at baseline and at 6 months*

	Surgery group n=32			Physiotherapy group n=35		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
PFDI scores, total	87.0 ± 45.8	45.1 ± 47.1	**<0.001**	93.7 ± 50.0	81.6 ± 53.1	0.06
POPDI-6 domain	30.6 ± 19.6	12.9 ± 17.2	**<0.001**	33.9 ± 20.7	27.9 ± 20.9	**0.02**
CRADI-8 domain	27.1 ± 18.8	14.1 ± 16.0	**<0.001**	27.5 ± 17.6	24.8 ± 18.2	0.2
UDI-6 domain	29.3 ± 20.9	18.1 ± 19.7	**0.004**	32.3 ± 23.8	28.9 ± 22.5	0.4
PFIQ scores, total	69.9 ± 56.2	26.8 ± 55.6	**<0.001**	63.1 ± 55.7	48.5 ± 41.6	0.1
UIQ-7	16.1 ± 22.4	6.5 ± 17.6	**0.003**	14.3 ± 20.9	12.7 ± 18.8	0.8
CRAIQ-7	20.8 ± 24.1	8.8 ± 19.8	**0.003**	18.0 ± 22.9	15.7 ± 20.1	0.8
POPIQ-7	33.0 ± 23.2	11.5 ± 21.8	**<0.001**	30.9 ± 21.4	20.0 ± 16.9	**0.003**
PISQ scores	31.5 ± 6.4	35.8 ± 7.4	**0.001**	32.7 ± 4.4	34.0 ± 4.7	**0.02**
HAD scores	11.1 ± 6.5	8.0 ± 7.5	**0.005**	12.2 ± 8.2	11.4 ± 6.3	0.4
Perineal body thickness (mm) on 2D ultrasound	7.9 ± 2.1	15.1 ± 2.7	**<0.001**	8.9 ± 2.3	9.0 ± 2.4	0.2
Perineal skin (pb) (cm)	1.8 ± 0.8	3.1 ± 0.5	**<0.001**	2.0 ± 0.6	2.1 ± 0.5	0.2
Genital hiatus (cm)	3.8 ± 0.6	2.9 ± 0.4	**<0.001**	3.6 ± 0.6	3.7 ± 0.6	0.3
Anterior vaginal wall (Ba) (cm)	-2.1 ± 0.7	-2.5 ± 0.7	**0.009**	-1.9 ± 0.8	-2.2 ± 0.8	**0.002**
Posterior vaginal wall (Bp) (cm)	-1.5 ± 1.2	-2.7 ± 0.7	**<0.001**	-1.6 ± 1.3	-1.5 ± 1.3	0.8
Cervix (C) (cm)	-6.6 ± 0.9	-7.2 ± 1.1	**0.02**	-6.6 ± 1.3	-6.5 ± 2.2	0.8
Total vaginal length (tvl) (cm)	8.8 ± 0.8	9.4 ± 1.1	**0.005**	8.8 ± 1.2	9.1 ± 1.1	**0.03**

* Pelvic floor distress inventory. Scores ranges from 0-300. POPDI = Pelvic organ prolapse distress inventory. CRADI = Colorectal-Anal distress inventory. UDI = Urinary distress inventory. Domain scores ranges from 0-100.

‡ Short form of pelvic floor impact questionnaire. Scores ranges from 0-300. UIQ = Urinary impact questionnaire. CRAIQ = Colorectal-Anal impact questionnaire. POPIQ = Pelvic organ prolapse impact questionnaire.

§ Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire. Scores ranges from 0-48.

|| Hospital anxiety and depression scale. Scores ranges from 0-21.

Changes in anatomical landmarks are reported in millimeters.

Within-group comparisons are analyzed with Wilcoxons test.

Table 13 shows a comparison of the delta value (follow-up value minus baseline value) between the two treatment groups. The surgery group was superior to the physiotherapy group in all aspects of symptom improvement. Table 14 demonstrates the frequency of different pelvic floor dysfunction symptoms before and after treatment. None of the patients reported de novo dysparunia.

Table 13. *Comparison of changes in secondary outcomes in the treatment groups.*

	Surgery group n=32	Physiotherapy group n=35	Original data	Imputed data
Changes in PFDI* scores, total	-42.0 ± 44.4	-12.1 ± 31.4	<0.001	0.001
POPDI-6 domain	-17.7 ± 21.4	-6.1 ± 14.1	0.02	0.01
CRADI-8 domain	-13.1 ± 16.5	-2.7 ± 12.5	0.003	0.003
UDI-6 domain	-11.2 ± 18.3	-3.3 ± 18.0	0.045	0.04
Changes in PIFQ‡ scores, total	-43.2 ± 49.9	-9.2 ± 31.1	<0.001	<0.001
UIQ-7 domain	-9.5 ± 19.2	0.3 ± 15.1	<0.001	0.02
CRAIQ-7 domain	-12.1 ± 20.9	-0.4 ± 15.3	0.003	0.009
POPIQ-7 domain	-21.6 ± 22.1	-9.1 ± 16.1	0.003	0.008
Changes in PISQ§ scores	5.1 ± 9.2	2.1 ± 4.4	0.025	0.08
Changes in HAD|| scores	-3.0 ± 5.6	-0.8 ± 6.5	0.04	0.047
Changes in perineal body thickness on 2D ultrasound (mm)	7.2 ± 3.1	0.1 ± 1.6	<0.001	<0.001
Changes in genital hiatus (Gh) (mm)	-8.3 ± 6.4	1.0 ± 5.3	<0.001	<0.001
Changes in anterior vaginal wall (Ba) (mm)	-6.1 ± 9.2	3.2 ± 14.2	<0.001	0.004
Changes in posterior vaginal wall (Bp) (mm)	-11.6 ± 13.9	0.3 ± 8.4	<0.001	<0.001
Changes in cervix (C) (mm)	5.4 ± 12.6	-0.9 ± 19.6	0.3	0.2
Changes in total vaginal length (tvl) (mm)	5.5 ± 9.6	4.1 ± 9.9	0.8	0.6

* Pelvic floor distress inventory. Scores ranges from 0-300. POPDI = Pelvic organ prolapse distress inventory. CRADI = Colorectal-Anal distress inventory. UDI = Urinary distress inventory. Domain scores ranges from 0-100.

‡ Short form of pelvic floor impact questionnaire. Scores ranges from 0-300. UIQ = Urinary impact questionnaire. CRAIQ = Colorectal-Anal impact questionnaire. POPIQ = Pelvic organ prolapse impact questionnaire.

§ Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire. Scores ranges from 0-48.

|| Hospital anxiety and depression scale. Scores ranges from 0-21.

Changes in anatomical landmarks are reported in millimeters.

In-between group comparisons are analyzed with Mann–Whitney U test.

Table 14. *Patient-reported pelvic floor dysfunction symptoms at baseline and at 6 months.*

Pelvic floor dysfunction symptoms	Surgery group			Physiotherapy group		
	Baseline n=35	Follow-up n=32		Baseline n=35	Follow-up n=35	
Do you usually experience pressure in the lower abdomen?*	16 (46)	5 (16)	0.01	15 (43)	17 (49)	NS
Do you usually experience heaviness or dullness in the lower abdomen?*	21 (60)	10 (31)	0.02	25 (71)	22 (63)	NS
Do you usually have a bulge or something falling out that you can see or feel in the vaginal area?*	17 (49)	4 (13)	0.002	18 (51)	18 (51)	NS
Do you usually have to push on the vagina or around the rectum to have a complete bowel movement?*	16 (46)	3 (9)	0.002	20 (57)	18 (51)	NS
Do you usually experience a feeling of incomplete bladder emptying?*	20 (57)	9 (28)	NS	17 (49)	12 (34)	NS
Do you ever have to push up in the vaginal area with your fingers to start or complete urination?*	2 (6)	2 (6)	NS	3 (9)	2 (6)	NS
Do you feel you need to strain too hard to have a bowel movement?*	20 (57)	6 (19)	0.002	21 (60)	21 (60)	NS
Do you feel you have not completely emptied your bowels at the end of a bowel movement?*	21 (60)	9 (28)	0.007	24 (69)	28 (80)	NS
Do you usually lose stool beyond your control if your stool is well formed?*	1 (3)	0 (0)	NS	1 (3)	1 (3)	NS
Do you usually lose stool beyond your control if you stool is loose or liquid?*	6 (17)	3 (9)	NS	2 (6)	4 (11)	NS
Do you usually lose gas from the rectum beyond your control?*	17 (49)	12 (38)	NS	17 (49)	16 (46)	NS
Do you usually have pain when you pass your stool?*	14 (40)	8 (25)	NS	13 (37)	13 (37)	NS
Do you experience a strong sense of urgency and have to rush to the bathroom to have a bowel movement? *	21 (60)	10 (31)	<0.001	23 (66)	17 (49)	NS
Does part of your bowel ever pass through the rectum and bulge outside during or after a bowel movement?*	4 (11)	3 (9)	NS	12 (34)	8 (23)	NS

Do you usually experience frequent urination?*	14 (40)	11 (34)	NS	21 (60)	22 (63)	NS
Do you usually experience urine leakage associated with a feeling of urgency; that is, a strong sensation of needing to go to the bathroom?*	14 (40)	5 (16)	0.007	12 (34)	10 (29)	NS
Do you usually experience urine leakage related to laughing, coughing, or sneezing?*	18 (51)	10 (31)	0.005	16 (46)	15 (43)	NS
Do you usually experience small amounts of urine leakage (that is, drops)?*	14 (40)	11 (34)	NS	13 (37.1)	12 (34.3)	NS
Do you usually experience difficulty emptying your bladder?*	8 (23)	7 (22)	NS	11 (31)	9 (26)	NS
Do you usually experience pain of discomfort in the lower abdomen or genital region?*	22 (63)	11 (34)	0.01	23 (66)	21 (60)	NS
Do you experience a sensation of a wide or open vagina, n (%)†			<0.001			NS
Never	0 (0)	17 (53)		1 (3)	1 (3)	
Sometimes	4 (12)	12 (38)		2 (6)	8 (23)	
Daily	28 (88)	3 (9)		32 (91)	26 (74)	
Do you experience air going in and out of the vagina , n (%)†			<0.001			NS
Never	3 (9)	14 (44)		2 (6)	5 (14)	
Sometimes	14 (44)	17 (53)		14 (40)	16 (46)	
Daily	15 (47)	1 (3)		19 (54)	14 (40)	
Do you experience excessive discharge , n (%)†			0.001			NS
Never	7 (22)	20 (63)		11 (31.5)	13 (37)	
Sometimes	17 (53)	9 (28)		11 (31.5)	12 (34)	
Daily	8 (25)	3 (9)		13 (37)	10 (29)	
Do you feel pain during sexual intercourse, n/total (%)‡			0.01			NS
No or seldom	9 (35)	20 (71)		14 (45)	13 (42)	
Sometimes	11 (42)	4 (14.5)		11 (36)	12 (39)	
Often or always	6 (23)	4 (14.5)		6 (19)	6 (19)	

* Questions from the Pelvic floor distress inventory questionnaire. Answers dichotomized from “no symptoms” or “no bother from symptom” to “no” and from ”mildly to greatly bothersome symptoms” into “yes”. Patients who reported “yes” are presented in the table.

† Non-validated questions.

‡ Question number 5 from the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire. In the surgery group a total of 26 patients answered the questionnaire at baseline and 28 at follow-up. The corresponding numbers in the physiotherapy group were 31 and 31.

Changes within groups are analyzed with McNemars test

6 DISCUSSION

6.1 THE RESULTS IN A CLINICAL CONTEXT

6.1.1 Study I

The main finding of this study was that using a slowly absorbable monofilament suture (for example PDS®) in anterior colporrhaphy, was associated with greater symptom relief and patient satisfaction at one year postoperatively as compared to a more rapidly absorbable multifilament suture (for example Vicryl®). A colporrhaphy procedure includes adaptation of fibromuscular tissue laterally in the vaginal sulci into the midline using sutures. Due to sparse evidence, there is no consensus on which suture material to use and the selection of suture material is often a decision of the operating surgeon.[66] A Cochrane review on abdominal wall closure techniques found that slowly absorbable monofilament sutures reduced the risk of incisional hernia when compared with multifilament sutures (RR 0.76, 95% CI 0.59-0.98).[129] It is, however, unclear whether results from abdominal fascia closure can be applied on pelvic floor fascial repair. A study by Goldstein et al comparing Panacryl®, Ethibond ®, Prolene® and PDS® found that braided sutures such as Ethibond® and Panacryl® had a much higher incidence of suture-related complications requiring treatment compared to monofilament sutures.[130] The study included both absorbable as well as permanent sutures. Non-absorbable sutures in the vagina have shown to cause problems such as suture erosion and repeat surgery due to suture removal.[131] Many pelvic floor surgeons are therefore prone to use absorbable sutures for midline plication.[67] The only previous study comparing PDS® and Vicryl® is a randomized controlled feasibility trial published in 2008 by Allahdin et al. They found no differences in prolapse symptom relief or quality of life scores between the groups at follow-up. The study, however, included a mix of anterior, posterior and paravaginal procedures as well as concomitant procedures (hysterectomy, incontinence surgery). It was a feasibility study and therefore not sufficiently powered to detect differences between the suture groups.

The most prevalent site for prolapse, and also for recurrence after surgical repair, is the anterior vaginal wall.[29,33,64] Clinically relevant definitions of cure, including absence of symptoms (subjective cure) or no prolapse beyond the hymen, results in cure rates ranging between 82-96%.[63] The number of cured patients in our study are thus comparable to previous studies where cure is defined as absence of vaginal bulging. The cure rate in the anterior colporrhaphy cohort was 78% in the SA suture group and 70% in the RA suture group. When changing the cut-off for cure, by grouping women with symptoms 1-3 times per month into “cured prolapse”, resulted in cure rates of 85% in the SA group and 75% in the RA group. Posterior colporrhaphy is not as prone to failure as the anterior wall. Anatomical cure rates in previous reports range between 76-96%.[132,133] Approximately 80% in both groups in our study reported absence of vaginal bulging at one year follow-up. We found no evidence supporting that the choice of suture material in posterior colporrhaphy

would matter. The intra-abdominal pressure on the surgical site might be lower on the posterior compartment compared to the anterior wall, which may explain why the tensile strength of the suture is not as crucial.[134]

Urinary symptoms such as incontinence, detrusor instability and obstructed urination often co-exist with prolapse but are not as specific to POP as vaginal bulging.[135] Both suture groups in the anterior cohort improved significantly regarding all urinary symptoms. However, urinary urge symptoms improved significantly more in the RA suture group. The association between POP and symptoms of OAB show contradictory results. Romanzi et al found that women with grade 3-4 cystoceles were more likely to have symptoms and signs of OAB compared to women with lesser degrees of prolapse.[136] In contrast, Burrows et al found that urgency and urgency urinary incontinence occurred more often in women with less advanced POP.[137] This was corroborated in another study using ultrasound to grade the severity of prolapse; women with higher grade of bladder prolapse were less likely to suffer from urge symptoms.[138] The RA suture group reporting less urgency at follow-up in our study might thus be explained by them having higher grades of postoperative prolapse.

Previous studies have reported a 20-50% prevalence of splinting at defecation among women with rectocele [50,133] and 24-76% prevalence of straining [50,139,140]. In our study, symptoms of obstructed defecation (straining and splinting) were more prevalent in women undergoing posterior compared to anterior repair. Approximately 40% in the posterior colporrhaphy cohort reported daily straining at defecation preoperatively and a significant reduction to 11% was seen postoperatively ($p<0.001$). The corresponding proportions of women reporting a daily need for manual assistance during defecation were 32% preop and 6% postop ($p<0.001$). Our findings that symptoms of obstructed defecation are more common in women with posterior compartment prolapse compared to other compartments, and that these symptoms improve after surgical correction of the anatomy, are similar to the findings in a study published in 2019 by Karjalainen et al.[52]

6.1.2 Study II

The main finding of this study was that cervical amputation cures symptoms related to POP equally well as vaginal hysterectomy (VH) in women with apical prolapse. Subjective cure, defined as the absence of vaginal bulging, was 81% in both groups and the satisfaction rate was even higher (89% in both groups). Equality between the two procedures was found in every strata of preoperative prolapse stage. The relative risk for severe complication was, however, ten times higher in the VH group compared to the cervical amputation group.

Uterine prolapse is a result of failed level I support, with damage to the cardinal and uterosacral ligaments.[22,141] The prevalence of objective uterine prolapse among postmenopausal women is 14%.[33] Previous studies have found that anterior vaginal wall and apical prolapse very often co-exist (figure 16),[142,143] which was evident in our study considering the fact that the majority of operations included a concomitant anterior colporrhaphy. However, isolated "one compartment only" defects do exist.[142]

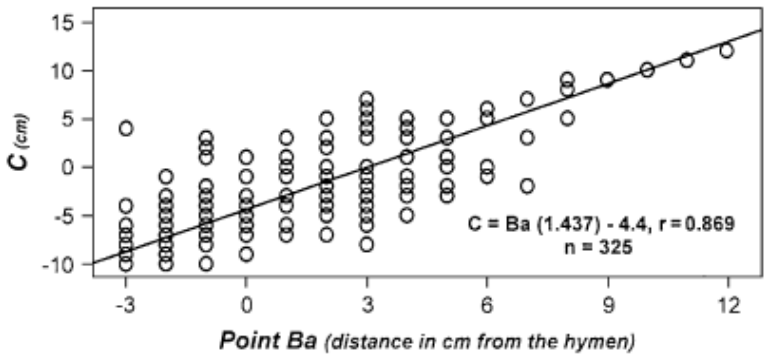


Figure 16. *Correlation between the anterior and apical compartment prolapse. Adopted from Rooney AJOG. 2006.*

There are many different surgical techniques to correct uterine decent and there is currently no consensus regarding the optimal approach.[144,145] Historically, VH is the most commonly performed procedure for uterine prolapse.[146,147] It has, however, been suggested that hysterectomy may cause damage to nerve supply and supportive structures of the pelvic floor increasing the rate of bladder dysfunction, SUI and POP recurrence.[148-150] A normal-sized uterus itself plays minimal role in apical decent, and the purpose of hysterectomy at time of POP surgery is to gain access to tissues used for apical suspension. A systematic review with meta-analysis on uterine preservation versus hysterectomy in POP surgery was published in 2018.[151] The authors found that uterine-preserving procedures improved operating time and blood loss, lowered complication rates and had similar short-term prolapse outcomes compared to vaginal hysterectomy. A study assessing patient preferences found that a higher proportion of women with prolapse symptoms preferred uterine preservation, compared with hysterectomy, provided that outcomes were equal.[152]

An argument for performing a hysterectomy solely due to prolapse, is that it eliminates the risk of an existing or future uterine or cervical malignancy. The prevalence of endometrial carcinoma in asymptomatic women undergoing hysterectomy for prolapse is 0.3-0-8.[153,154] This is in line with a study by Koss et al who discovered a 0.7% prevalence of endometrial carcinomas diagnosed with endometrial biopsy in a screening program in 2,586 peri and postmenopausal

women.[155] The background risk of incidental cancer in asymptomatic women is thus low. A preoperative workup with a Pap smear and endometrial ultrasound, plus an endometrial biopsy when indicated, could be an option in women with POP where uterine preservation is planned.

The Manchester procedure (MP) was first performed in 1888 and originally included amputation of the cervix combined with an anterior and posterior colporrhaphy. In 1921 Fothergill modified the technique by suturing the cardinal ligaments on to the cervical stump. In 2018 Oversand et al published a prospective cohort study on 153 women who underwent the Manchester procedure in a Norweigan clinic, with a follow-up rate of 97% at one year postoperatively.[156] The procedure included an anterior colporrhaphy, cervical amputation and uterosacral/cardinal ligament shortening and plication proximal to the anterior part of the cervix stump. A perineal body reconstruction was performed in all cases. POP-Q stage < 2 was obtained in 99% in the mid-compartment but only in 49% in the anterior compartment. 5.6% reported de novo dyspareunia and 96% reported being cured or significantly improved. Previous studies comparing MP with VH are summarized in a review article by Tolstrup et al, published in 2017.[157] It included nine studies of which one was a randomized controlled trial. Both anatomical recurrence rates for the middle compartment and re-operation rates were higher after VH compared to MP. VH was associated with more perioperative bleeding, longer operating time and more bladder lesions and infections, which is in line with the findings of our study. The same authors published a matched cohort study in 2018 on the same subject including patients with POP treated with VH (n=295) or MP (n=295).[158] The risk for prolapse in any compartment was higher after VH (18.3%) compared with the MP (7.8%) with a HR of 2.5 (95% CI 1.3-4.8). There were more perioperative complications (2.7 vs. 0%, p = 0.007) and postoperative intra-abdominal bleeding (2 vs. 0%, p = 0.03) after VH. The superiority of the MP in comparison to VH was also found in a recently published study based on data from the Danish register for gynecological surgery.[159] The reason why we did not find superior outcomes in the CA group in our study may be that the women did not undergo the "full Manchester repair" which includes also posterior colporrhaphy. Further, the Forthergill technique, which includes suspension of the apex by suturing the cardinal ligaments to the cervical stump, might not be performed by all surgeons performing CA in Sweden.

Other uterine preserving techniques for apical prolapse are sacrospinosus ligament fixation (SSLF) and abdominal (laparoscopic/robotic) sacrohysteropexy. Two meta-analysis analyzing results of SSLF concluded that the pooled apical failure rate (POPQ grade ³2) was 8.5-10% [160,161] and 13% were dissatisfied with the result[161]. The pooled failure rate after SSLF in the anterior and posterior compartment were 21-35% and 6-7% respectively. SSLF performs equally well in comparison to VH considering apical failure and re-operation rates.[160] The rate of

visceral injuries during a SSLF was as low as 0.4%.[160] The most common complication after SSLF is buttock pain. It often resolves spontaneously but 4% have persisting symptoms 4–6 weeks postoperatively.[162] Both laparoscopic and robot-assisted sacrohysteropexies have excellent cure rates, objective ranging between 91-94% and subjective between 92-95%.[70] These procedures, however, require both high-technology operating facilities, as well as experienced surgeons, and comes with a median mesh erosion rate of 2-5% .[163,164]

In summary, there are many different surgical treatment options in women with a prolapse of the middle compartment. No guidelines currently exist to guide the choice of technique. Procedures including removal of the uterus comes with a higher rate of serious complications and trends are turning to uterus preserving procedures in women with uterine decent. Sacrohysteropexies have the highest reported success rates but require high-technology operating facilities and experienced surgeons. This procedure also comes with higher costs, longer operation times and a low but yet existing risk of mesh erosions. The Manchester-Fothergill operation is a minimally invasive procedure with satisfactory results and low complication rates as compared to VH and should be considered a valid option.

6.1.3 Study III

The main finding of this study was that women who gave birth after a mid-urethral sling procedure (MUS) did not have a higher rate of SUI, or other urinary symptoms, compared to women with no deliveries after their MUS procedure. Furthermore, continence status was not affected by the mode of a subsequent delivery.

Due to lack of evidence, most physicians have previously recommended delaying incontinence surgery until childbearing has been completed .[103] Many have even advocated cesarean delivery to a pregnant women with a previous MUS procedure.[165] The most recent review article is published by Cavkaytar et al in 2015 including 66 women with a delivery after a MUS procedure (53% by cesarean section and 47% by vaginal delivery).[107] The authors found no difference in postpartum incontinence when comparing mode of delivery after a MUS. The prevalence of incontinence postpartum was 20%, which is similar to our study where 22% of the women with a delivery after a MUS reported SUI. In 2016 Adams-Piper et al. published the so far largest case series of women with a delivery after a MUS procedure, which included 26 cases.[104] This study corroborated the findings of the safety and durability of a MUS after a subsequent pregnancy and delivery.

In 2019, one year after our study was published, Dyrkorn et al published a Norwegian study very similar to ours, which allows for interesting comparisons.[166] Their study included 72 women (39 vaginal deliveries, 33 cesarean sections) with and 156 without childbirth after a MUS procedure. The median follow-up time was 10 years

after the initial MUS procedure, as compared to 9 years in our study. The primary outcome was absence of SUI, defined as having a SUI index of 0 in a validated condition specific questionnaire. A strength of the study was that they had data on continence status 6-12 months after the initial MUS procedure, which allows for comparison of symptoms before and after the subsequent delivery. Subjective cure rate of SUI was 82% in the "childbirth after MUS" group and 75% in the "no childbirth after MUS" group, p=0.31. When stratifying for one versus multiple deliveries after the MUS procedure, the authors found a significantly increased the risk of SUI in the multiple deliveries group (50% versus 88%, p=0.006). Mode of delivery after MUS surgery did not affect the outcomes, which is in line with the findings of our study. The "childbirth after MUS" group had a subjective cure rate of 93% at 6-12 months after their initial MUS procedure, which dropped to 88% after one subsequent delivery (p=0.3) and to 84% when including also the women with multiple deliveries after their MUS procedure (p=0.04). The change in SUI cure rates in the control group was non-significant (dropped from 77% at 6-12 months to 75% at 10 years postoperatively). In our study 3/163 (1.8%) women reported a need for bladder catheterization during the pregnancy where she had a MUS in place compared to 1/72 (1.4%) in the Norwegian study.

Obesity is a well-established risk factor for urinary incontinence.[1] However, studies investigating whether obesity is a risk factor for failure after MUS surgery show contradictory results.[167-171] Both the present study and the Norwegian study found that a BMI over 30 correlated with significantly higher odds of patient reported SUI. Another risk factor for persisting SUI symptoms, found in both our and the Norwegian study, was repeat surgery for SUI. These findings are in accordance with previous studies. Stav and co-workers compared outcomes in 1,035 women with a primary MUS procedure and 77 women with a repeat MUS procedure.[172] The subjective stress incontinence cure rate was 86% and 62% in the primary and repeat group, respectively ($p < 0.001$). A systematic review of the literature on procedures for recurrent SUI was published in 2015 and included 52 studies.[173] The common characteristic of all procedures for recurrent SUI was a lower success rate compared to the primary procedure. Repeat mid-urethral sling procedures had a pooled success rate of 66.2% (95% CI ±4). In our study, the subjective success rate in women with a repeat sling procedure was 68%. We also found that women with self-reported psychiatric illness had a significantly higher rate of subjective SUI. Many authors have found a correlation between anxiety/depressive disorders and urinary incontinence.[174,175] Causality and temporal order are however unclear.

The effect of pregnancy and delivery on outcomes of MUS surgery can, for obvious reasons, never be tested in a randomized trial. The evidence guiding practice must therefore rely on observational studies. In summary, current evidence which is based on multiple case series and two relatively large cohort studies with matched

controls, do not find results indicating that at least one subsequent pregnancy jeopardizes the results from a previous MUS procedure. Neither do they find evidence that cesarean section is protective of SUI recurrence in women with a MUS.

6.1.4 Study IV

The aim of Study IV was to evaluate and compare surgical and conservative treatment in women with loss of level III support due to grade two perineal injuries. The results showed that surgical treatment leads to higher patient-reported global improvement rates. Surgery was also superior in curing pelvic floor and sexual dysfunction symptoms, as well as improving quality of life and psychological symptoms at 6 months after treatment.

There are a numerous amount of studies reporting outcomes of posterior compartment procedures and they often mention perineorrhaphy being performed as a part of the operation when indicated. Kanter et al conducted a survey among gynecologic surgeons attending the annual "Society of Gynecologic Surgeons" meeting in 2014, regarding factors of importance when deciding to perform a perineorrhaphy and details of their surgical technique.[110] The authors found heterogeneity of practice patterns, both in terms of reasons for performing a perineorrhaphy and techniques for doing so. Many consider the perineal body to consist of the transverse perineal and bulbocavernosus muscles distal to the hymen. A total of 60% of the responders noted that they perform levator muscle plication or attach the rectovaginal septum to the perineal body.

Previous studies on perineal reconstructive surgery focus mainly on cosmetic outcomes and sexual enhancement.[176] Validated questionnaires assessing pelvic floor dysfunction symptoms have not been used and no studies include a control group, which limits comparisons. Ulubay et al. described anatomical changes, patient satisfaction and sexual function in 38 women undergoing perineorrhaphy due to "a sensation of a wide vagina".[111] The patient satisfaction rate was 88% in comparison to 80% in the per-protocol analysis of the patients who underwent perineorrhaphy in our study. Christmann-Schmid et al published a study of 121 patients undergoing posterior repair where preoperative perineal anatomy was categorized into three groups; normal perineum, short perineum and high/overcompensated perineum.[177] The study included 16 women with a short perineum (pb <2.5 cm) where the authors performed a posterior colporrhaphy plus a perineorrhaphy. The surgical technique included a diamond shaped excision of the perineal skin and mucosa distal to the hymen and surgically merging the detached perineal body structures to the midline. Patient reported treatment success, according to the Patient Global Impression of Improvement, was 95% at 6 weeks. However, they found no reduction in dyspareunia rates.

Dyspareunia is a known complication of vaginal surgery but it seems like a defectively healed perineal body by itself is a risk factor for dyspareunia. Painful sexual intercourse was reported "often" or "always" by 42% of the patients included in our study compared to a prevalence of 7.5% in the general population.[178] Studies have shown that the degree of perineal trauma during childbirth is correlated to the degree of dyspareunia at short term.[179,180] Previous studies show conflicting results regarding de novo dyspareunia following posterior compartment procedures.[181] Secondary perineal repair has been shown to improve dyspareunia in a small cohort of women who developed postpartum dyspareunia after initial obstetric repair.[182] A total of 10% in the study by Ulubay et al reported de novo dyspareunia. Inan et al. studied changes in Female Sexual Function Index (FSFI) scores in 40 women undergoing perineoplasty.[113] The technique included excision of scar tissue in the perineum, placing of bilateral levator ani sutures and approximation of the superficial transverse perineal and the bulbocavernosus muscles. The sexual function scores improved significantly, which is in concordance with our study, but they found no significant reduction in dyspareunia rates. Somewhat surprisingly, none of the patients undergoing surgery in our study reported de novo dyspareunia. Instead a total of 17/26 (65%) reported presence of dyspareunia sometimes, often or always preoperatively and only 8/28 (29%) postoperatively (p=0.01). Contributing to the low rate of de novo dyspareunia in our study compared to previous mentioned studies may be; minimal dissection when aiming to identify the disrupted perineal muscle ends, avoiding excessive excision of skin or mucosa distal to the hymen and not applying levator ani sutures.[183]

The perineal membrane is intimately associated with the compressor urethrae and the urethrovaginal sphincter.[18] An intact perineal body seems to be important in maintaining urinary continence.[13] In total, 34/70 (49%) of the women included in our study reported moderately to greatly bothersome SUI at baseline. We found a significant reduction of SUI from 51% to 31% (p=0.005) 6 months after surgery. The results from this study thus supports a two-step approach, where a mid-urethral sling procedure could be postponed to a secondary operation in those patients with persisting bothersome SUI. Somewhat surprisingly, urinary symptoms did not improve significantly following physiotherapy, which is contradictory to many previous studies.[101] This discrepancy could be explained by an insufficient sample size in our study. It could also be that women with perineal body defects cannot contract the muscles surrounding the urethra as effectively as women with an intact perineum.

The lower one-third of the posterior vagina is fused with the perineal body. Separation of fibers in the perineal body leaves the rectum unsupported and results in a low posterior prolapse.[184] The anal canal may bulge and protrude out of the vaginal opening during defecation. At inclusion 16/35 (51%) in the surgery group reported that they have to push on the vagina or around the rectum to have a com-

plete bowel movement. This number was reduced to 3/32 (9.4%) at 6 months after surgery but remained unchanged in the physiotherapy group. Other symptoms of obstructed defecation, like straining and feeling of incomplete emptying, were also highly prevalent in the study population but diminished significantly in the group receiving surgical correction of the anatomy. The prevalence of anal incontinence 5 years after childbirth in women without a third or fourth degree tear has been reported to be as high as 32%.[185] Flatus incontinence was reported by 49% of the study participants in our study, which is not surprising considering the intimate relationship between grade 2 perineal muscles and the anal sphincter complex. The rate of flatus incontinence decreased to 37.5% in the surgery group, but the reduction did not reach statistical significance. This could be explained either by the low sample size or the fact that anal incontinence is not always related to muscle defects but to neurologic impairment.[186]

In conclusion, surgical compared to conservative treatment, was significantly and considerably more effective in women with second degree perineal defects after childbirth. Perineorrhaphy seems to reduce most pelvic floor dysfunction symptoms, as well as, improve quality of life, sexual functions and psychological well-being, in women these women. The surgical technique (type of incision, removal of perineal skin or no, placing levator ani sutures or no) is, however, not standardized and future trials are needed to find the optimal approach.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Internal validity – systematic error

Selection bias and misclassification

The study participants in **Study I, II and III** are selected from nationwide population-based registers with excellent coverage and thus include the majority of patients in the source population. This minimizes bias occurring from how patients enter the studies. In all three studies the response rates might, however, introduce some degree of selection bias. Even though there is not one single cut off for a response rate that would secure unbiased results [187], as a general rule, response rates above 80% are considered good, while those between 60 and 80% are acceptable.[188] Previous studies have concluded that non-responders have less severe symptoms.[189,190] The response rates in **Study I-III** were 66%, 78% and 74% respectively. In all three studies, we performed a "non-responder analysis", by comparing all demographic characteristics and exposure status between the responders and non-responders. We did not find any differences between the two groups.

Missing values of possible confounding variables can also introduce selection bias.[191]

Study I had considerable problems regarding missing data. Important possible confounding factors had substantial proportions of missing values; BMI (23%), parity (22%), menopausal status (49%) and preoperative sensation of vaginal bulging (19%). When we were in the process of building a regression model to control for possible confounding we lost almost half of our study subjects. We therefore adjusted for only age and ASA class in the main analysis and used the other variables in a regression model as a sensitivity analysis. After our study was published, many new reports on risk factors for prolapse recurrence are available. Using the updated knowledge about risk factors, we performed further sensitivity analyses with regression models including all known risk factors that were available in the dataset. This regression model had however 25% missing cases. A complete case analysis implicitly assumes that observations are missing completely at random, which cannot be assumed. We therefore performed an additional analysis with multiple imputation of missing values. None of the sensitivity analyses did however significantly alter the results.

The primary outcome in both **Study I and II** was cured prolapse defined as patient-reported absence of vaginal bulging symptoms at the 1-year follow-up questionnaire. The question "Do you experience a feeling of something bulging out of your vagina?" was dichotomized from five answer options (never or almost never into "no" and 1–3 times per month, 1–3 times per week or daily into "yes"). This question is validated for assessing symptomatic prolapse [125,192] and an affirmative answer has shown to have a 84-96% sensitivity and 79-94% specificity for prolapse beyond the hymen.[193,194] It has also been found to have the strongest correlation with patient-reported improvement and treatment success.[60] However, the optimal cut-off for cured and persisting clinically significant prolapse in unknown. We initially chose to categorize 1-3 times per month into treatment failure, whereas Bohlin et al categorized this into "no prolapse".[117]

One could also question the choice of vaginal bulging being our primary outcome when assessing cure after posterior colporrhaphy, since vaginal bulging might not be as specific for women with posterior prolapse. Common problems associated with a rectocele are symptoms related to obstructive defecation.[43,50,52,132] Ellerkman et al reported, however, that bulging symptoms were the most specific symptom among women with prolapse regardless of compartment and the correlation between visualizing a bulge was as strong in the posterior as in the anterior compartment.[43] In our study, vaginal bulging was the most common symptom preoperatively (77-79%). Further, we found no differences between the suture groups when comparing overall patient satisfaction or any of the symptoms related to obstructive defecation.

Co-variates such as degree of prolapse and ASA class could possibly include some degree of misclassification since we don´t know if all surgeons reporting to the

register correctly classifies the degree of prolapse according to the standardized way described in the POP-Q system[34] and some gynecological surgeons may not be entirely familiar with all the criteria in the ASA classification system. It is also possible that adverse events are underreported in the register. Also patient reported co-variates, such as weight, height and parity and especially smoking status, may include misclassification. However, we find no arguments for these misclassifications having a high probability of being differential.

The primary outcome in **Study III** (symptomatic SUI) is measured with a validated tool, the UDI. UDI and IIQ-7 questionnaires are "highly recommended" by the ICS as robust and appropriate questionnaires for evaluating symptoms and the quality-of-life effect of UI.[127] Patients answering moderately to greatly bothersome symptoms on the question number three of the UDI ("Do you experience urine leakage related to physical activity, coughing or sneezing?") correlate excellently to objective SUI in urodynamic testing.[126] Milsom et al. identified 356 women who reported UI based on a postal survey and had them evaluated by clinicians who were blinded to the questionnaire responses. UI was confirmed by objective assessment in 94%, indicating that determine urinary incontinence by the questionnaire criteria is very likely to be clinically relevant.[195]

In **Study IV** the exposures were pelvic floor muscle training compared to surgery. The group allocated to physiotherapy did receive coaching and evaluation of correct muscle training technique from trained health care professionals, but we did not measure if the patients actually performed the recommended muscle exercises. Nonadherence may thus lead to differential misclassification of the exposure. There is currently no validated objective outcome that defines success in treating women with symptomatic perineal defects and there is not one specific pelvic floor dysfunction symptom that is validated to determine cure versus treatment failure in this group of patients (in analogy with bulging sensation in women with POP). We therefore chose to use patient-reported global assessment of improvement (PGI). This outcome has gained increasing popularity as an important outcome in pelvic floor dysfunction research when assessing results of treatments. It has shown to strongly correlate with treatment success regarding management of other pelvic floor disorders.[196,197] For obvious reasons the treatment allocation could not be blinded, which to some extent may introduce placebo effects. Since our primary outcome was purely subjective, patient expectations of symptom relief is likely to be affected by if the she was assigned to the treatment she was hoping for or believed in.

The definition of a perineal defect is also not standardized. The height of the perineal body in adult nulliparous women, according to the definition of the POP-Q system, ranges between 3.1-4.1 cm.[198,199] We therefore chose to include women

with a perineal body height of <2cm in order to maximize the likelihood of the study subjects having anatomic defects of the perineum (34% had a perineal body height <1 cm and 66% less than 2 cm). The lack of nonblinded outcome assessment may have caused measurement bias.

Confounding

In **Study I** we used logistic regression in order to control for possible confounding factors. The regression models has been discussed in detail in previous chapters. Possible confounding variables that we haven't been able to adjust for are for example the specific suturing technique, continuous or interrupted suturing and the number of sutures used in the mid-line plication. We did not adjust for surgeons experience, however, a recent study assessing surgical experience and results of single site, primary colporrhaphy procedures found no such association.[200] We did not have data on other possibly important confounders such as levator ani injuries and genetic or hereditary factors.

"Confounding by indication" is a term used when a variable is associated with the exposure status and at the same time a risk factor for the outcome. In **Study II**, there is a substantial risk for confounding by indication, since the presence of a cervical elongation, and not true apical decent, might be the reason for choosing cervical amputation instead of hysterectomy. Patients with only cervical elongation and adequate level I support, are probably less likely to suffer from recurrence. The register data unfortunately does not provide information about the presence of possible cervical elongation. Using the definition corpus uteri/cervix ratio of < 1.5 for cervical elongation [201], Berger et al found that cervical elongation was present in 98 % of patients undergoing hysterectomy due to objective and symptomatic uterine POP stage II–IV. This suggests that the majority of the patients in our study in both groups had some degree of cervical elongation.

In **Study II** the database did unfortunately not contain valid information regarding how and if a suspension of the cuff/stump was performed during the surgical procedures, which could be an important confounding factor. Since preoperative prolapse stage is a strong risk factor for the outcome, we also tested the robustness of our results in strata of the four different grades of prolapse.

In **Study IV** we used randomization to control for confounding, which is considered as the optimal approach to eliminate confounding. This design optimizes the probability of known and unknown confounders being distributed equally in both groups. However, it is worth noting that RCTs are not without their own biases, as illustrated by the "intent-to-treat" approach, where study participants are considered exposed to the assigned treatment, regardless of actual compliance. The intent-to-treat analyses can minimize a real difference, generating bias towards the null.

6.2.2 Precision

The precision in **Study I** and especially in **Study II** must be regarded as high due to the large sample size and a relatively high prevalence of the outcome (bulging at one year). This is reflected by the narrow CIs. However, when trying to adjust for multiple possible confounders in **Study I**, the sample size was reduced by 50% due to missing values in different variables, which remarkably lowered the precision of the estimates. The large sample size in **Study II** abled us to detect differences in rare outcomes, such as severe complications. Whether the negative results in **Study III** are explained by type II error is an inevitable question. We performed an a priori power calculation and the final sample size reached the desired level of power needed to detect a clinically relevant difference between the exposed and unexposed groups. We therefore argue that the risk of a type II error is low. The subgroup analysis of vaginal versus cesarean section after a MUS procedure might however lack sufficient power, although the difference in percentage points was zero (22% versus 22%), which strongly suggests that there is no difference between the groups. The sample size in **Study IV** is relatively small but nonetheless adequate, taking into consideration the large difference between the groups regarding the primary outcome. Interpretation of results of secondary outcomes must however be made with caution.

6.2.3 External validity

External validity reflects whether the conclusions of a scientific study can be applied outside the context of that study. In other words, it is the extent to which the results of a study can be generalized to other groups of peoples or settings. A crucial and often neglected variable in studies assessing outcomes after any surgical procedure is the experience and skills of the surgeon.[202] A meta-analysis examining the associations between operating volume and outcomes found a positive correlation regarding hysterectomies, gynecological oncology, surgical mesh complications, and incontinence procedures.[203] The study participants in **Study I, II and III** are sampled from nation-wide registers, which have a strong external validity by the fact that they have high coverage and include "typical patients". They often include more heterogeneous populations than those participating in RCTs (wide variety of age, ethnicity, and comorbidities). Especially when assessing outcomes of surgical procedures, register data can provide a good description of the true impact of interventions in actual practice, and not only in patients treated by few expert surgeons. The operating clinics varied from large-scale teaching hospitals to smaller private practices. In **Study I** and **II** we excluded secondary procedures, which limits the conclusions to patients undergoing primary procedures.

In **Study III** the majority of women had given birth only once after their MUS procedure, and thus conclusions cannot be generalized to women with multiple births after their incontinence procedure. **Study IV** is a single-center randomized trial, which limits the external validity. The procedures were performed by one of five different urogynecologists according to a structured protocol, and the pelvic floor muscle therapy sessions were tutored by two different physiotherapist. The results of the interventions are likely to be different when performed in other centers. We excluded for example women with connective tissue disorders, current use of systemic corticosteroids, diabetes mellitus and women who had undergone previous pelvic floor surgery. The mean age of the study population was 35 years, which limits generalization of outcomes of the procedure to older or postmenopausal women.

7 CONCLUSIONS

The conclusions of the studies included in this thesis are:

I. The use of a slowly absorbable monofilament suture is associated with significantly higher odds of cured prolapse symptoms and higher rate of patient satisfaction one year after anterior colporrhaphy, as compared to the use of a more rapidly absorbable multifilament suture. The choice of suture material does not seem to affect patient-reported outcomes after posterior colporrhaphy.

II. Cervical amputaion seems to cure prolapse symptoms at one year after surgery as effectively as complete removal of the uterus, in women with apical decent. However, vaginal hysterectomy is associated with a higher rate of severe complications and perioperative morbidity.

III. One preganancy and delivery after a mid-urethral sling operation does not seem to jeopardize the results from the incontinence procedure. The mode of the delivery subsequently to the incontinence procedure does not seem to have an impact on postdelivery continence status.

IV. Surgical correction of the anatomy in women with a poorly healed second degree perienal tear at least six months after childbirth, is considerably more effective then tutored physiotherapy in curing pelvic floor and sexual dysfunction symptoms. The surgical technique evaluated in this study does not seem to increase the risk of de novo dysparunia.

8 ETHICAL CONSIDERATIONS

All four studies in this thesis were reviewed and approved by Regional Board of Ethics in Stockholm, Sweden (Dnr 2014/958-31/4 and Dnr 2015/1101-31/4). All data was handled according to regulations in the Personal Data Act in Sweden (Swedish abbreviation: PUL). Data were anonymized and handled following recommendations for good clinical practice in data management. Results from all studies in this thesis are presented at an aggregated level.

According to Swedish law, research conducted using anonymized data retrieved from national registers can be used without informed consent from the study subjects. In **Study I-II**, data from the GynOp register was delivered as anonymized data and individual patients could not be identified. Patients receive written information about the register when scheduled for surgery and they have an opportunity to decline participation in the register. Patients also have the right to demand their personal information to be erased from the register.

For **Study III**, the Swedish National Board of Health and Welfare conducted the linkage between the National Patient Register and the Medical Birth Register, in order to identify the eligible study population. The research question would not have been possible to answer without contacting the possible study subjects. Personal identity codes were therefore shared with the researcher in order to allow for postal questionnaires. Written informed consent was, however, obtained from the study participants in conjunction with the postal questionnaire. All electronic datasets containing personal identifiable information were password protected and only accessible to researchers involved in the study. For data entry and analyses, personal identity codes were substituted with unidentifiable codes.

In **Study IV**, oral and written information was provided to the patients invited to participate in the study. Randomization was performed after informed written consent was obtained from the patient. Both treatments are a part of clinical practice for women with perineal defects. Participating in the study only means that one or the other treatment is randomly provided first. If the patient has persisting symptoms at the 6 month follow-up she could cross-over to receive the other treatment. Further, participation in the study was completely voluntary and the patients were informed that they could drop out of the study, without explanation, if they would regret participation.

9 FURTHER PERSPECTIVES

The anterior vaginal wall is the most common site for prolapse and techniques using native tissue are the first line approach in surgical management of this condition. Considering the high failure rates after anterior colporrhaphy, it is crucial to conduct well-designed trials guiding evidence based standardization of technical details of this procedure. Prospective randomized trials with long-term follow-up are needed to confirm the associations found in Study I. Another unexplored surgical detail is whether continuous versus interrupted suturing technique has an impact on the outcome.

Anterior and apical compartment prolapse often co-exist. Future studies are warranted to define which patients benefit from concomitant apical suspension. For example, in a woman presenting with primary anterior prolapse reaching just below the hymen and with a cervix that comes down to – 4 cm; what does the long-term risk-benefit ratio look like if an apical suspension procedure is added to the anterior colporrhaphy.

One can choose from a variety of surgical procedures when treating women with apical prolapse. There are currently no evidence-based guidelines to aid the surgeon in this selection process. Two large randomized trials exploring surgical techniques when treating women with apical prolapse are currently ongoing in the Netherlands; one comparing laparoscopic sacrocolpopexy with sacrospinosus fixation in women with vault prolapse and one comparing the modified Manchester operation with sacrospinosus hysteropexy. Randomized trials comparing sacrohysteropexy with the Manchester-Forthergill procedure, as well as cost-effectiveness analyses, are needed to provide further evidence for the choice of uterus sparing procedures in women with apical decent.

Regarding women with perineal defects there are multiple unanswered research questions. What is the optimal surgical technique when balancing symptom relief and the risk of dyspareunia? Should deeper levator ani sutures be used or not? The methodologies to study this group of patients need to be standardized and validated. A questionnaire designed to capture the symptomatology in women with grad 2 perineal defects is under the process of validation by a Swedish research group. Also studies assessing the normal and abnormal anatomy of the perineum using 3-dimensional ultrasound are ongoing. The results from these trials will be useful in order to fully describe the symptomatology and anatomy before and after surgical repair.

10 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bäckenbottendysfunktion innefattar symptom kopplat till framfall, urin- och avföringsinkontinens. Förekomsten av symptomgivande framfall uppskattas till 6% och cirka 20% av kvinnor genomgår bäckenbottenkirurgi på grund av framfall eller inkontinens under sin livstid. Framfall innebär att lilla bäckenets inre organ, så som urinblåsa, livmoder och tarm, förlorar sitt stöd och buktar ner mot eller ut genom slidöppningen. Det vanligaste symptomet hos kvinnor med framfall är just en känsla av att något buktar ut ur slidan. Tyvärr får en betydande andel av kvinnorna återfall trots framfallsoperation. Det saknas kunskap kring optimala kirurgiska tekniker för att hitta en bra balans mellan bot och potentiella komplikationer. En tämligen ostuderad subgrupp av kvinnor med bäckenbottendysfunktion är kvinnor med kvarstående skador på mellangården (perinealkroppen) som uppkommit i samband med en vaginal förlossning . Så kallad ”defektläkt perinealkropp” kan innebära att muskler som stödjer slidöppningen och tarmen tappat sitt fäste och därmed även sin funktion.

Ansträngningsinkontinens innebär att muskler och vävnad som stödjer urinröret, helt eller delvis, förlorat sin funktion. Detta leder till att man inte lyckas stå emot eller kompensera för ett ökat tryck i bukhålan som uppstår vid t ex ansträngning, hosta eller nysning, vilket leder till ofrivilligt läckage av urin i samband med dessa situationer. Den vanligaste riskfaktorn för att utveckla ansträngningsinkontinens är vaginal förlossning och symptomen debuterar ofta efter att kvinnan fött sitt första barn. Det finns en effektiv kirurgisk behandling där man opererar in en stödjande nätslynga under urinröret (TVT operation) och upp till 80% upplever bot efter denna operation. Det saknats dock kunskap om effekten av nätslyngan förstörs av en efterföljande graviditet, samt om gravida kvinnor med ett inkontinensband skall rådas till att föda vaginalt eller med kejsarsnitt.

I denna avhandling har vi undersökt om valet av suturmaterial påverkar resultatet av en framfallsoperation. Vi har även studerat om kapande av enbart livmodertappen (cervix amputation) leder till symptomlindring i lika stor utsträckning som borttagande av hela livmodern hos kvinnor med livmoderframfall. Vi har också undersökt om resultatet av en TVT operation påverkas av en efterföljande förlossning. Slutligen har vi studerat symptom före och efter kirurgisk jämfört med konservativ behandling, hos kvinnor som drabbats av en defektläkt grad två bristning efter en vaginal förlossning.

Studie I och **II** är baserade på data inhämtat ut det nationella kvalitetsregistret för gynekologisk kirurgi, det så kallade GynOp registret. I **Studie I** ingick 230 kvinnor med framfall av främre vaginalväggen där kirurgen använde långsamt

absorberande monofilament sutur (LAS) och 501 där man använde snabbare absorberande multifilament sutur (SAS). En signifikant lägre andel kvinnor i LAS gruppen rapporterade en känsla av att något buktar ut ur slidan vid ett år efter operationen, 22% jämfört med 30% (p=0.01). I LAS gruppen var även en högre andel kvinnor nöjda med resultatet, 83% jämfört med 75% (p=0.03). Hos kvinnor som opererades för framfall av bakre vaginalväggen spelade valet av suturmaterial ingen roll för symptom vid ettårsuppföljningen.

I **Studie II** undersökte vi resultat efter ett år hos 3174 kvinnor som opererats på grund av livmoderframfall. Totalt 1979 kvinnor där enbart livmodertappen kapats (cervixamputation) jämfördes med 1195 där hela livmodern bortopererades via slidan (vaginal hysterektomi). I bägge grupperna hade man hos majoriteten även gjort en samtidig framväggsplastik, eftersom livmoder- och framväggsframfall ofta samvarierar. Vi fann lika goda resultat i bägge grupper avseende bäckenbottensymptom och patientnöjdhet vid ettårsuppföljningen. Däremot drabbades färre kvinnor i cervixamputationsgruppen av allvarliga kirurgiska komplikationer, 0.2 jämfört med 2%. Cervixamputationsgruppen hade även kortare operations-, återhämtnings- och vårdtid samt mindre blödningsmängd.

I **Studie III** länkade vi uppgifter från det nationella patientregistret med det medicinska födelseregistret för att identifiera kvinnor som fött barn efter en TVT operation. Ur samma register identifierades även en kontrollgrupp, matchad för ålder och operationsår, där kvinnorna inte fött barn efter sin TVT-operation. Vi skickade ut validerade frågeformulär till bägge grupper för att kartlägga förekomsten av urinsymptom. Vi identifierade 207 kvinnor som fött minst ett barn efter en TVT-operation och 521 kontroller. Totalt 74% svarade på vår enkät. Vi fann ingen signifikant skillnad mellan grupperna avseende förekomst av ansträngningsinkontinens eller övriga urinsymptom. Vi fann heller inga skillnader mellan kvinnor som fött vaginalt och med kejsarsnitt efter en TVT-operation. Detta talar för att effekten av nätslyngan består om man föder ett barn efter sin operation och att man inte behöver rekommendera kejsarsnitt till denna grupp.

I **Studie IV** inkluderades totalt 70 kvinnor med symptomgivande, defektläkta grad två bristningar, där det gått minst sex månader efter den senaste förlossningen. Hälften lottades till handledd bäckenbottenträning och hälften till kirurgisk rekonstruktion, så kallad perineorafi med distal bakre plastik. De vanligaste symptomen hos de inkluderade kvinnorna var vaginal vidhetskänsla, slidpruttar och tarmtömningsbesvär, där kvinnorna var tvungna att trycka med ett finger i slidan eller mot mellangården för att kunna tömma tarmen. Vid uppföljningen efter 6 månader rapporterade signifikant fler i kirurgigruppen att de var mycket eller väldigt mycket förbättrade. Kirurgi var överlägsen konservativ behandling i att bota de flesta symptom inklusive samlagssmärta.

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